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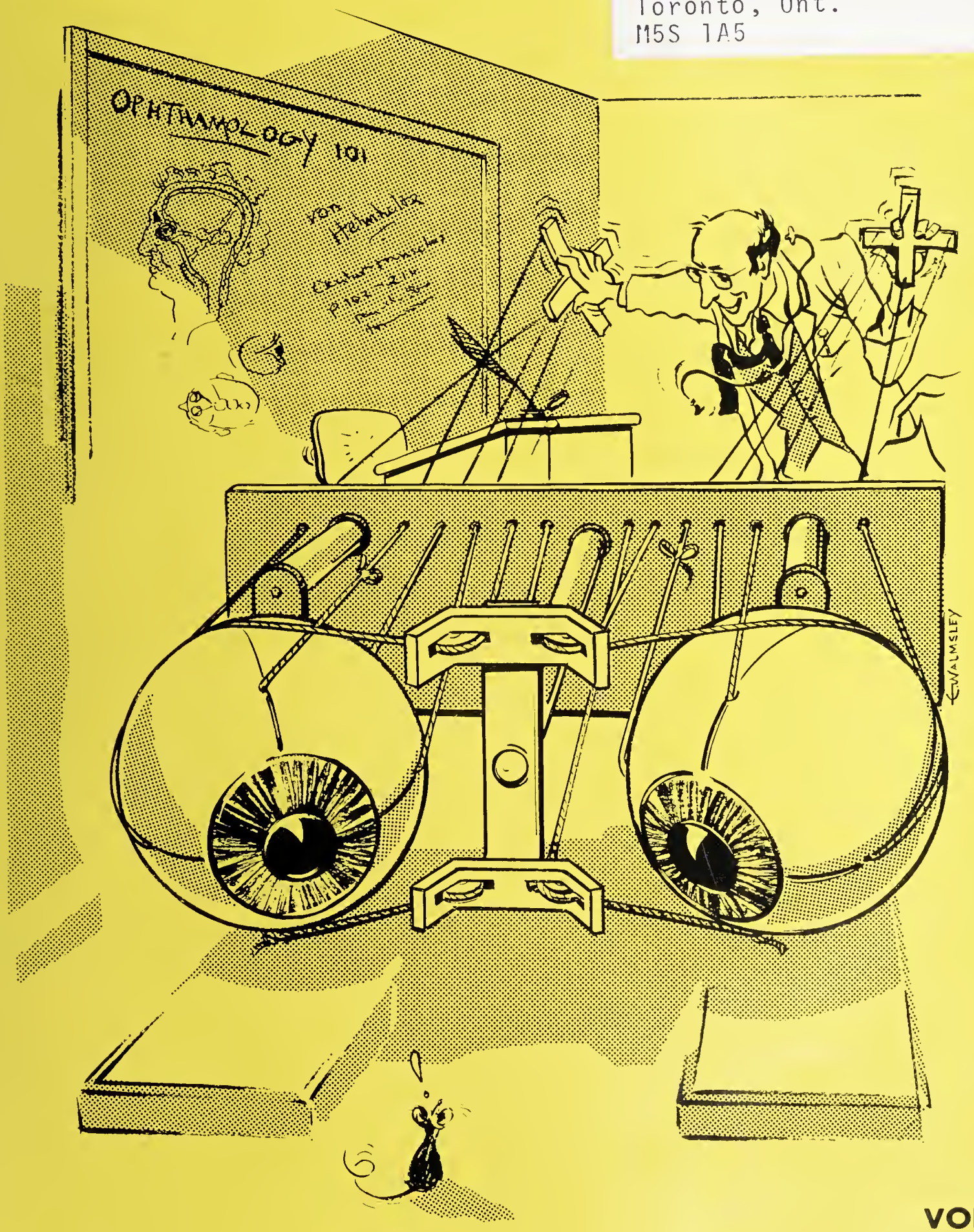

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GUIDELINES FOR PUBLICATION

1) All articles intended for publication should be submitted to the editors before the deadline which is usually six weeks before the release of the Journal
2) Submitted articles should be typed (or legibly printed) double-spaced single sided on paper 8½" x 11 (letter size) and they should not be more than 15 to 20 pages (3000 to 4000 words)
3) Illustrations, graphs diagrams and figures should be put on a separate sheet and identified by Arabic numerals A list of explanatory legends for all the figures and diagrams should be put on another sheet Do not write on the back of photographs
4) References should be checked with the original sources, designated by Arabic numerals in the text, numbered in order of appearance and put on a separate sheet Each periodical reference should include in order the author's name and initials, title of the article, Journal name volume number, page number and year (eg 1 Rosen HJ Lumbar invertebral disc surgery review of 300 cases *Can Med Assoc J 101 317 1969*)
5) The editors reserve the right to make such editorial changes as are deemed necessary to ensure correctness of grammar and spelling, clarification of statements and conformity to Journal style
6) Acceptance for publication is subject to the understanding that such material is submitted solely to the Journal and will not be reprinted without the consent of both the editors and author

Front Cover: An actual demonstration model of the eye made by Herman von Helmholtz in 1807.

The Doctor's Hospital

Bruce Menchions 8T3

The complicated structure of the modern tertiary-care hospital imposes unexpected constraints on the unwary physician. With reference to a variety of concepts from organizational theory and economics, this article describes one aspect of observable behaviour in this system and points to the need for greater physician participation in hospital management.

A relatively new decision technique called Cost-Effectiveness Analysis is introduced as one method of moving toward this integration.

A hospital is much more complex than an overgrown private medical practice. While its primary goal is to improve the health of the surrounding population by employing the best of present-day technical-medical knowledge, it must carry out this function subject to a great number of constraints dictated by finite human, physical, and financial resources. Often overlooked is the limitation imposed by our incomplete understanding of how to put together, and successfully maintain, such specialized and interdependent human activity.

What role do physicians play in this scenario, and how well does conventional medical education prepare them for their part? While it is true that most of the M.D. curriculum is devoted to "medical-technical knowledge", there remains until later the discovery, mostly by trial and error, of the hospital organization as a creature by itself, with its own goals and incentives which at times can be very different from those of the medical staff. Here, we can briefly examine this organization by drawing on an assortment of ideas from organizational theory and organizational economics, using a nine-month case study of an Ontario tertiary-care hospital as a backdrop. Finally, a promising decision tool called "cost-effectiveness analysis" will reveal insight into a greater participation by physicians in the managing of the hospital organization.

Where Did Hospitals Come From?

Although Christianity is often given credit for originating formal, organized hospitals, both Hindus and Greeks had much earlier planned and administered aid for their sick. By about the 12th Century, medical practice began to assume a scientific cause-and-effect basis apart from its earlier ecclesiastic principles. Thereafter, large hospitals in the capitals of Europe began to flourish, advancing the causes of medical practice, teaching, and research. The beneficial role of hospitals in curing disease was dramatically increased by the 19th-Century discovery of antibiotics. In the present century, hospitals in this country have been the recipients of vast public financing from all levels of government. While there is a range of religious and professional histories in Ontario tertiary-care hospitals, most today have similar organizations.[1]

How Are They Organized?

On paper, most of the authority and responsibility within the hospital are vested in two groups: the medical staff and the administrators. The medical staff is organized by specialty usually with a chief physician in major departments such as Medicine, and is overseen by a body frequently called the Medical Advisory Committee. Administrators are similarly departmentalized, and the most influential department directors typically constitute a more central Executive Committee. Ostensibly, both the physicians and the administrators are responsible to the community-sponsored Board of Governors through the chief administrator. The monthly Board meetings are heavily influenced, however, by recommendations from the physicians and the administrators.

The entrance of a patient into the hospital triggers a vast array of very specialized responses from the people in the organization: clinical clerks, dieticians, anaesthetists, computer programmers, carpenters, surgeons, nurses, and many others participate in the organization's activity.

The idea of harmonious effort is not new, nor is it unique to humans. In *The Iliad*, Homer observed that "When many are got together, you can be guided by him whose counsel is wisest...If a man is alone he is less full of resource, and his wit is weaker." Throughout recorded history man has used organizations for tasks as simple as growing corn, and as complex as manned space flight. Bankers, flamingos, and whales all exhibit organizational behaviour.

In the widely-held holistic view of organization, it is a major problem to co-ordinate and motivate all the people within to work at least

generally in the direction of organizational goals. Not only do people constitute the system, they also react to its existence (hence, for instance, industrial sabotage). The whole field of Organization Theory has developed as the study of how and why people behave as they do in organizations. As both sociology and psychology have become more sophisticated, so too has organization theory.

In the late 19th Century, Frederick W. Taylor founded a school which believed that workers could be treated as machines. Max Weber later incorporated the notion of a well-defined hierarchy with rule and systems into a normative description of organizations. The famous but controversial experiments at the Hawthorne Plant of the Western Electric Company showed that people react to their environments, and that behaviour can be modified by manipulation of environmental variables. Researchers subsequently contributed much greater understanding of human needs, perception, learning, motivation, and leadership within the setting of an organization, and identified the importance of stimuli both inside and outside the organization.

And The People?

Here, only generalizations can be made about the groups within the hospital, but they can lead to some interesting observations.

The physicians comprising the medical staff are the most dominant group in the determination of the day-to-day treatment of patients. Most of the hospital's resources are placed directly or indirectly at the discretion of the medical staff. Administrators, nurses, electricians, and all the other members of the organization have distinct roles in the longer run, but without the daily activity of the physicians, the hospital would soon flounder.

Physicians are responsible first and foremost to their patients. Medical care is administered almost exclusively on a personal basis, especially in critical situations. Since life is considered a basic right for all individuals within our society, then a very high personal standard is set for those who deliver this care. The Hippocratic Oath designates the improvement of the patient's health as the supreme priority. This oath may be likened to an agency contract between society in general and physicians: in return for high professional competence and conduct, an opportunity is afforded to earn high monetary returns and achieve a high level of social status. Except in the case of the physician's gross negligence, once the medical services are provided, he or she is answerable to no one outside the professional ranks.

The physician's contract with society specifically excludes cost as a direct factor in his or her decision-making. Some researchers deny that this is an artifact of a system, like OHIP, of complete public medical insurance. But whichever premise applies, physicians are free to ply their daily trade within the hospital framework generally irrespective of the cost to the hospital of their actions.

The second major group within the hospital is the collection of administrators (usually not physicians) from the level of executive director down to the directors and department heads. These people are charged with maintaining the complete array of ancillary services supplied by the hospital for use by physicians (and teachers): nursing, nutrition, various clinical departments, laboratories, and so on, as well as support services such as housekeeping and purely administrative functions such as accounting, admissions, and finance. More so than physicians, who have a very strong professional association, administrators are perhaps more sensitive to influences outside the hospital milieu. In Ontario the process of hospital global budgeting has effectively given a lot of managerial clout to the Ministry of Health which supplies the vast majority of hospital income. Specifically, the Ministry has put severe real economic constraints on the hospitals' operating budgets, and the activity of hospital administrators has—in marked contrast to physicians—become quite focused on cost-saving.

The Board of Governors in an Ontario hospital is a diverse group which includes representatives from outside the hospital as well as from within. Its role in the hospital has become more formal than effective, but ostensibly it is necessary to win the Board's approval for all major decisions in the hospital, such as altering the operating budget or approving capital expenditures.

Of course, for all three groups just described, there are many non-monetary motivators such as peer recognition, institutional prestige, working conditions, desire for leisure time, and stress minimization, all of which are factors in individual goal-oriented behaviour.

How Do They Work?

This description of the hospital can be simplified further into the model of a dual hierarchy—one medical, and the other administrative. Several studies have found this to be a fairly accurate representation.[1] [2] The behaviour of the administrative hierarchy is powerfully influenced by an external influence, the Ministry of Health, which is currently manipulating hospital funding to induce a greater cost-consciousness on the part of administrators. The medical hierarchy, however, responds largely to its own professional standards, irrespective of other influences except for its agency contract with society. As earlier described, on a day-to-day basis, physicians have effective control over hospital resource allocation because it is they who decide which drugs, food, specialized nursing care, lab tests, operating rooms, and so on will be used. In short, it really *is* the Doctor's hospital.

Organizational economists have an enlightening view of the hospital. They liken it to a marketplace—rather than a formal organization[3]—with buyers and sellers, much like the Toronto Stock Exchange.

In the hospital marketplace, expertise is supplied by the physician, and physicial resources (drugs, laboratories, beds, operating theatres, and so on) by the administrator. When the sick patients "demands" care, both the physician and the administrator must respond

(continued on page 101)

The Study Of Glomerulonephritis

Michael Cusimano 8T4

Glomerulonephritis may be manifested as either a primary or secondary disease. Classification is by histology obtained from renal biopsies. Much remains unknown with respect to etiology, natural history and response to drug treatment due to lack of properly controlled prospective studies. The Metropolitan Toronto Glomerulonephritis Registry, now supervising five controlled trials, was formed in 1974 with the aim of closing some of those gaps in our knowledge. A general review of the glomerulonephritides is made throughout the paper.

The term glomerulonephritis (GN) covers many renal diseases, mostly of unknown etiology but having in common glomerular histological abnormalities.

The glomerulonephritides may be primary (kidneys alone affected) or secondary (part of a systematic disease). Each primary type has its own history, clinical presentation (or lack of it) and associated response to therapy.

GN is the leading cause of terminal renal failure in the Western world.[1,2,3] It is reported to be responsible for up to 65% of end-stage renal disease cases and is four times more prevalent than pyelonephritis, the second commonest cause.

The Registry

In an attempt to overcome the shortcomings of small single hospital-based research studies (where limitations are placed on conclusions by small sample groups[4] and the often difficult-to-interpret international studies[5], the Glomerulonephritis Registry of Metropolitan Toronto (the Registry) was set up in the summer of 1974.

The Registry serves as the central office for the supervision of clinical drug trials. It also serves as a storage and analysis facility for data accumulated on the 1500 patients registered since 1974. The data provides:

(a) a base for properly controlled prospective drug trials;

(b) a tool to study the natural history of GN;

(c) a stimulus for future study of the etiology and epidemiology of GN; and,

(d) an educational experience for referring internists, nephrologists and family practitioners.

The process of data collection and analysis, shown in Figure 1, is a complex one depending on nephrologists, pathologists, family physicians, statisticians and computer consultants working in close cooperation with the GN Registrar. The Registrar is the most important person in the Registry scheme, as she is responsible for the collation and processing of the mass of data obtained. Table 1 outlines the number and types of biopsy-proven cases of GN documented from August 1974 to May 1979. This data reaffirms the belief that proper systematic studies of GN can be carried out in a prospective fashion with maximal physician and patient cooperation.

The Clinical Trials

Since numbers were sufficiently large for clinical trials to be started, a central committee of hospital representatives was formed to establish protocols for suitable drug trials. Ethical approval was obtained from the University of Toronto, and since then five trials have been started and are running simultaneously. Briefly, these are trials in Mesangiocapillary GN, Focal Sclerosing GN, Membranous GN, Idiopathic Crescentic GN and Disseminated Lupus Erythematosus. The first three of these have now reached the analysis stage. Simultaneously date has been collected on other subgroups including IgA Nephritis, Diffuse Proliferative GN, the other collagen vascular diseases and Focal Proliferative GN.

Mesangiocapillary GN

The clinical presentation of mesangiocapillary GN ranges from microscopic hematuria to rapidly progressive renal failure. Overall five-year kidney survival is in the range of 60-75% with a subsequent rapid decline resulting in a ten-year survival of 20%. Features of nephrotic syndrome or renal insufficiency at the time of initial diagnosis may indicate a bad prognosis.

On light microscopy, there is a thickening of the basement membranes with proliferation of mesangial cells and mesangial matrix, giving the glomerulus the lobular appearance seen in Figure 2.

Electron micrscopy allows definite histological division into two types. Type 1 is associated with subendothelial deposits and normal or low

Table 1: Breakdown of the numbers and types of almost 1200 cases of biopsy proven glomerulonephritis documented from August, 1974 to May, 1979.

Type	Prior to 1974	1974	1975	1976	1977	1978	Total
Minimal change	--	11	10	21	6	4	52
Membranous	5	9	27	19	25	18	103
Mesangiocapillary	3	15	18	24	16	3	79
Proliferative	7	17	38	48	44	21	175
Focal Sclerosing	2	10	15	37	25	12	101
IgA (Berger's)	--	5	13	28	22	10	78
Focal proliferative	--	9	25	24	25	7	91
Rapidly progressive	--	2	8	11	10	3	34
Lupus	--	9	33	35	24	14	115
Collagen disease	--	2	5	8	4	2	21
Chronic	--	7	12	12	2	2	35
Other	16	9	55	69	72	83	304
	33	105	259	336	276	179	1,186

complement levels (Figure 3); while type 2 has extremely low complement levels and dense deposits outlying the capillary lumina.

An uncontrolled study by Kincaid-Smith[6] suggested that a combination of cyclophosphamide, 2-3mg/kg; Coumadin (an anticoagulant); and dipyridamole (an anti-platelet agent), 100 mg q.i.d. for 12 months improved the overall long-term survival of these patients. However, in the Toronto study (with almost 60 cases), initial results have tended to contradict those of Kincaid-Smith.

Focal Sclerosing GN

Focal Sclerosing GN (or Focal Glomerular Sclerosis, FGS) is commonly mistaken for "Minimal Change GN" because in unaffected glomeruli, there is no difference in pathology. In both FGS and Minimal Change, the patient usually presents with the nephrotic syndrome and normal creatinine clearance. The clue to a diagnosis of FGS may be the presence of hypertension, increased serum creatinine or numerous red blood cells in the urine sediment. Slight differences are also evident on electron microscopy.

Minimal Change GN accounts for about 70% of cases of the nephrotic syndrome in children and from 15-20% in the adult population. Steroid therapy given as prednisone (60 mg/m² on alternate days for 28 days, followed by 40 mg/m² q2d for a subsequent four weeks) is commonly used and is effective in 80-90% of patients.[7] Oral cyclophosphamide alone, or in combination with prednisone, is also effective in about 50-60% of the "non-steroid responders" or "frequent-relapse" group[8 9 10]. The number of patients with FGS responding to the preceding regimens is often much lower. But a trial of therapy is probably indicated because in several years these patients often progress to renal failure[11]. Although the Registry's drug trial study of FGS may be one of the largest in the world, no conclusions have been reached as to the efficacy of anti-platelet agents versus no therapy over a 12 month period.

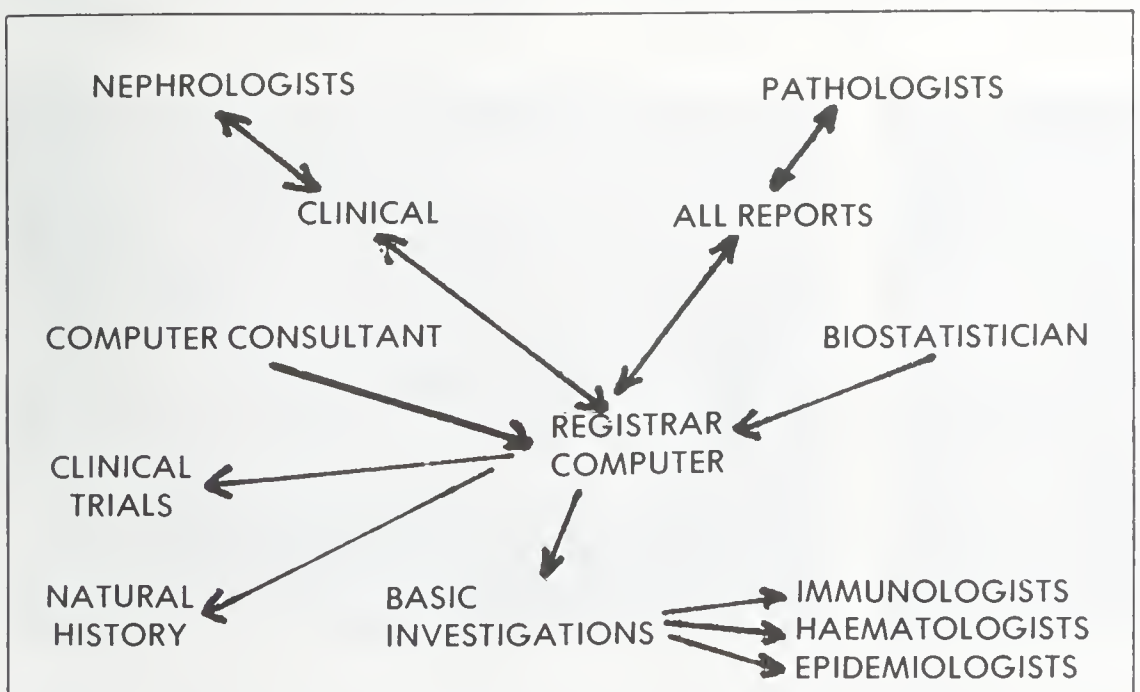

Figure 1: Basic structure of the Metropolitan Toronto Glomerulonephritis Registry. The Registrar is the main pivotal point in the scheme.

Membranous GN

Idiopathic membranous GN is the single most common lesion producing the nephrotic syndrome in the adult. Most patients present between the ages of 40 and 60 with a definite male predominance of 2:1. 10% of Lupus Nephritis patients in North America present with the same picture as the idiopathic group. The idiopathic group, histologically, shows diffuse capillary basement membrane thickening (Figure 4) on light microscopy, and on EM, small subepithelial deposits. Immunofluorescence staining is positive for IgG and B_1C complement.

Classically, the clinical course of

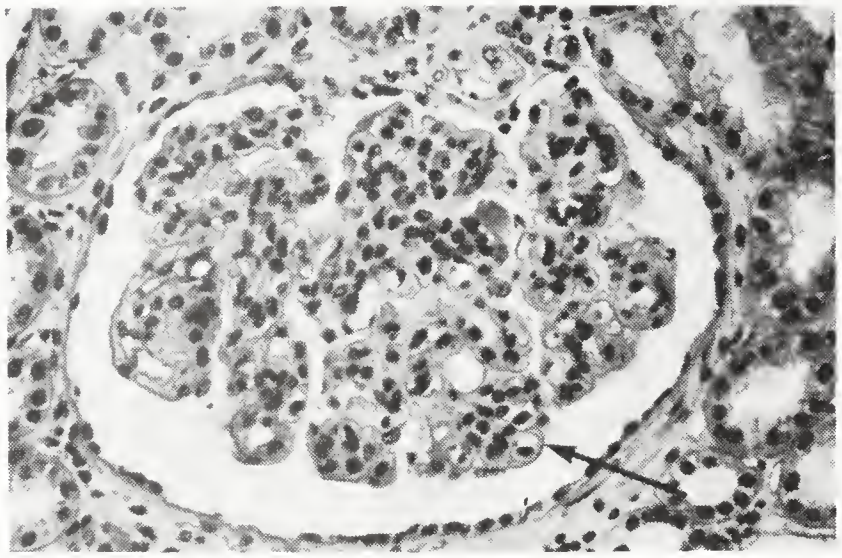

Figure 2: The light microscope appearance of Mesangiocapillary GN. Peripheral capillary loops are thickened and may show double contours (arrow). H&E 400X

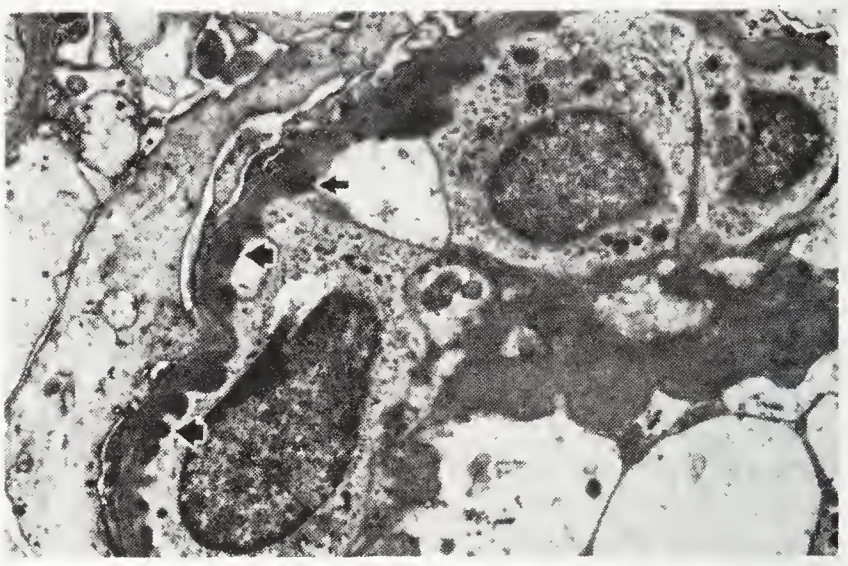

Figure 3: Type I Mesangiocapillary GN. Subendothelial electron-dense granular deposits (arrow). H&E 1700X

these patients falls into three distinct categories—1/3 of the patients develop spontaneous remission, 1/3 have steady proteinuria and the nephrotic syndrome, and 1/3 show a slowly progressive deterioration in renal function over a number of years. Consequently, obtaining a suitable control group displaying all types of clinical courses (ie. the 1/3:1/3:1/3 breakdown) is imperative if controlled prospective trials in biopsy-proven membranous GN are to have any meaning. In the Boston Cooperative Study Group Report on the efficacy of short-term Prednisone therapy[12], the extremely poor prognosis of the control group detracted from the general applicability of the publicized reports. A suitable control group is still being formed for the Toronto study on the long-term effects of a six-month course of moderate dose, alternate-day steroids on the proteinuria and creatinine clearance in these patients.

Crescentic GN

Classically, the pathological lesions observed in Crescentic (Rapidly Progressive) GN include widespread epithelial proliferation and crescent formation as well as fibrin deposition within both the crescents and the glomerular loops (Figure 5). Spontaneous recovery is unlikely if more than 85% of glomeruli have crescents; whereas patients with a definite history of previous streptococcus infection or those in whom less than 50% of glomeruli have crescents seem to have a better prognosis. Symptomatic management is usually advised but immunosuppressive drugs are often given in an attempt to modify the rapidly deteriorating clinical course. Polyarteritis Nodosa, Wegener's Granulomatosis, Goodpasture's Syndrome, Scleroderma and Henoch-Schonlein Nephritis often give clinical presentations associated with Crescentic GN.

A drug trial observing the effects of bolus Solu-Medrol (methylprednisolone) on the ultimate outcome in patients with Idiopathic Crescentic GN is now being conducted by the Registry.

Diffuse Proliferative GN

Although the most common known cause of primary Diffuse Proliferative GN is a streptococcal infection, this only accounts for up to 20% of adult cases. Histologically, light microscopy shows generalized diffuse hypercellularity of the glomeruli including an increased number of polymorphs and/or mesangial cells. Severe cases may

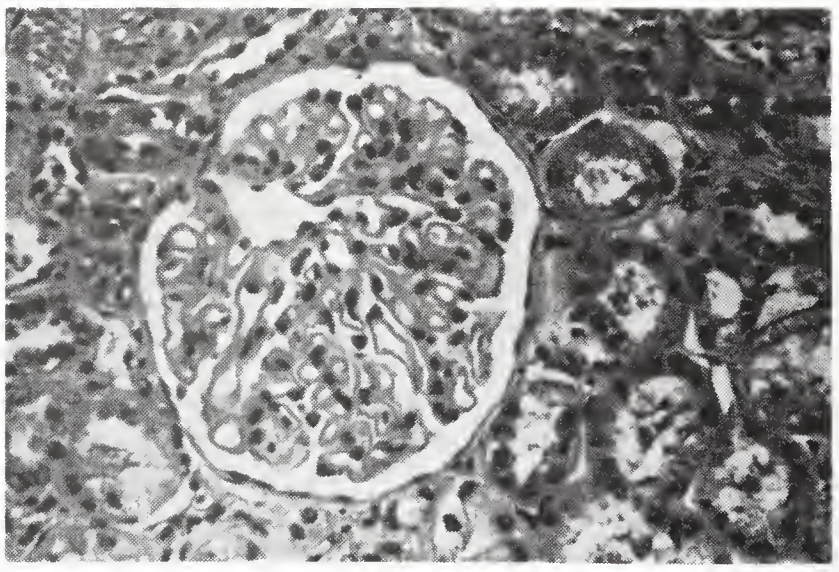

Figure 4: Diffuse thickening of the glomerular capillary basement membrane without increased cellularity in Membranous GN. H&E 250X

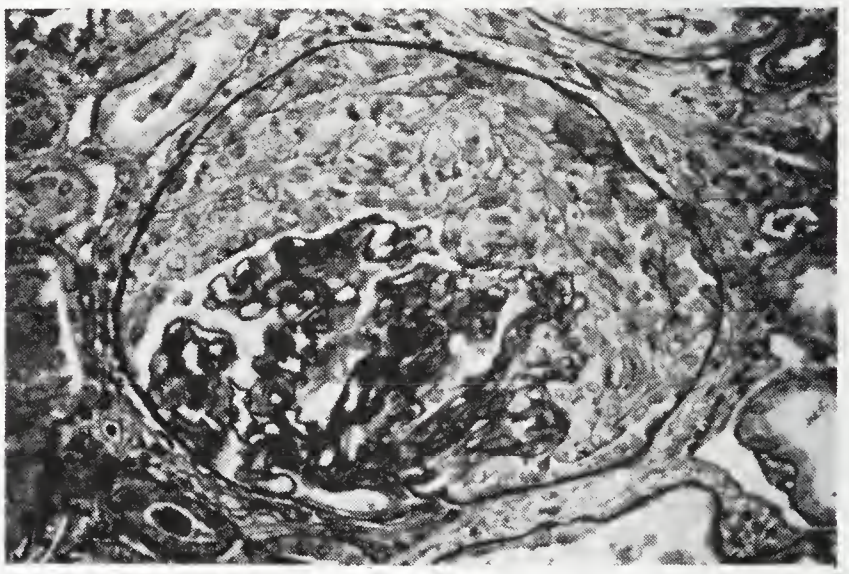

Figure 5: Rapidly progressive GN. A severely affected glomerulus showing a circumferential cellular crescent producing occlusion and compression of the glomerular tuft. PAS 400X

show epithelial crescents. The EM shows electron-dense subepithelial deposits early in the disease and IgG and B_1C are seen in an interrupted "granular" pattern on immunofluorescence.

Patients may present with gross proteinuria, microscopic hematuria or Rapidly Progressive GN. However, approximately 80% will recover spontaneously, with 20-30% of patients developing end-stage renal failure after a 20-25 year chronic smouldering course. Patients are usually treated symptomatically for complications such as edema or hypertension. At present, there are approximately 200 cases of biopsy-proven Proliferative GN.

Focal Proliferative GN

Patients with Focal Proliferative GN (IgA/IgG Nephritis, Berger's Disease) most often present with a history of recurrent gross hematuria usually following an upper respiratory infection, extreme exertion or exposure to extreme cold. Only 5-10% of patients have deteriorating renal function over many years, while most follow a benign course which usually warrants no special therapy[14 15].

Lupus Nephritis

The fifth drug trial presently under way in Toronto is looking at the effects of periodic plasmapheresis in conjunction with steroid therapy in patients with Proliferative Lupus Nephritis.

Lupus Nephritis produces a variety of renal histological lesions; 60-70% show diffuse proliferative changes; 10-20% membranous changes; 10-30% focal proliferative changes; and 5-10% mesangial abnormalities.

Renal involvement clinically may be manifested by some patients as an abnormal urine sediment while a few show rapidly progressive renal failure. Therapy is usually aimed at obtaining a normal urinalysis, normal renal function, and correction of serologic abnormalities. Most patients with both diffuse proliferative and membranous involvements are started on 80-120mg of prednisone daily to control renal inflammation[16]. The addition of azothioprine in an attempt to lower the steroid dose has not been shown to be efficacious[16]. Focal proliferative renal involvement usually indicates an excellent prognosis and treatment is directed at extrarenal signs of the disease. Mesangial Lupus may change in morphological form to a diffuse proliferative or membranous lesion and therefore may merit early therapy[17].

Conclusion

GN may be either a primary or secondary disease. Classification is based upon histology as little is known about etiology, natural history and response to drug treatment. The studies now being carried out by the Metropolitan Toronto Glomerulonephritis Registry will help to close these gaps in our knowledge. □

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Epidemiologic Factors Associated With Ocular Hypertension

John Christakis 8T2

Many epidemiologic factors have been associated with ocular hypertension. Some of these factors, will be discussed in an attempt to focus on controversial and inconsistent associations. Some speculation will also be made as to how these risk factors relate to ocular hypertension.

Most physicians will consider a patient to have ocular hypertension if the intraocular readings are persistently above 22 mm Hg, provided that there is no central scotoma, optic disc pallor with excavation, or change in visual acuity.[1] [2] The pressures of most ocular hypertensive patients will change with time, however, it is generally felt that an increasing pressure trend is an important symptom indicating a higher risk of developing glaucoma. Therefore, it is of clinical interest to identify factors associated with ocular hypertension, and to recognize those patients with trends of increasing pressure as early as possible so that they may be followed up and treated appropriately.

Ocular Factors

Several authors have noted that there is a strong association between refractive error and intraocular pressure (IOP).[3] [4] [5] The IOP of emmetropes is higher than that of hyperopes, while myopes have a higher IOP then emmetropes. Not surprisingly, it has been shown that the IOP increases with the axial length of the eye, the most significant difference being between myopes (15.59 mm Hg) and emmetropes (14.74 mm Hg).[4] Some authors[6] believe that myopia is actually secondary to an increased IOP which stretches the eye. However, others take the opposite point of view, that the distensibility of the sclera in myopia compromises the outflow system and increases outflow resistance. The significant difference in IOP between myopes and emmetropes is also due to biological variations related to the structure and thickness of the cornea, accommodation, and the volume of the eye.

Studies[7] have shown a greater increase in IOP among ocular hypertensives following fluid provocative testing than among controls. This can be attributed to the fact that the sclera is maximally distended in the ocular hypertensives and can no longer expand, thus causing a greater rise in pressure.

Age

Many studies have shown age to be strongly associated with ocular hypertension. Although in some studies the reported results did not exclude patients with ophthalmologic abnormalities, most (with similar results) excluded patients with active uveitis, glaucomatous field defects and other ophthalmologic abnormalities.[6] [7] [8] [9] Colton and Ederer found that there was greater than 1 mm Hg mean difference in IOP between males in their twenties and seventies, and greater than 3 mm Hg difference between females in these age groups. Ganley speculated that this difference could be related to fibrotic changes in the trabecular meshwork which increases with age, or perhaps, could be due to decreased pinocytic activity of the endothelial cells at the level of Schlemm's canal.[6]

Sex

There is a higher incidence of ocular hypertension in females. Armaly[8] pointed out that the increase in the female to male ratio becomes quite evident during the menopause with its accompanying hormonal changes. Paterson and Miller[10] found the aqueous outflow to be greatest during the first quarter of the menstrual cycle when serum estrogen levels are elevated, or when serum levels of both estrogen and progesterone are increased during the third quarter of the menstrual cycle. They feel that the changes in IOP are due to a pressure lowering effect of estrogen and progesterone, and therefore, the climacteric decrease in estrogen and progesterone may account for the IOP elevation in post-menopausal women.

Systolic Blood Pressure

Bulpitt[11] found a 2 mm Hg increase in IOP for every 100 mm Hg in systolic blood pressure. His explanation for this elevation in IOP was that the systolic compression of the central retinal vein by the accompanying artery causes increased vascular resistance. It has also been shown that many patients with open-angle glaucoma have a higher systolic blood pressure than the rest of the population. In these patients, the raised IOP is probably due to the higher perfusion pressure in the ciliary arteries, increasing the filtration of aqueous fluid in the ciliary body. In support of this, Linner has shown a correlation between elevated systolic blood pressure and higher rate of aqueous flow.[12]

Diabetes

With the high incidence of arteriosclerosis and small vessel disease in diabetics, one would intuitively expect an increased incidence of ocular hypertension in diabetics over the normal population. Traisman et al.[13] found a mean IOP of 24.05 mm Hg among their juvenile diabetics who had a blood sugar of 200 mg% or more. Among their juvenile diabetics who had a blood sugar of less than 200 mg%, they found a mean IOP of 21.4 mm Hg (as compared to the 17.7 mm Hg of their control group). Some studies show a similar increase of IOP among adult onset diabetics, as compared to controls. Surprisingly, they also found that diabetics with retinopathy had lower IOP (14.5 mm Hg) than those without retinopathy (19.7 mm Hg).[14]

Gragoudas, Bouzas and Balodimos[15] in their study from the Joslin Clinic found no association of ocular hypertension with the diabetic state, or even with the duration of disease.

Other Factors

Obesity is another factor which can be related to ocular hypertension. This is probably due to depositions of lipid at the angle of the anterior chamber, obstructing aqueous drainage.

Corticosteroids tend to decrease aqueous outflow, possibly through accumulation of glycosaminoglycans in the trabecular meshwork. Topically applied steroids given in high concentration over several weeks may also cause an increase in IOP to the "glaucoma range".[16] However, in experiments when cortisol secretion was suppressed by dexamethasone, there was no change in IOP[8], suggesting that the relationship between cortisol and increased IOP may be only correlative and not causative.

The hematocrit is theoretically important, as resistance in the episcleral veins can be increased by rises in blood viscosity. However, to date, although glaucoma has been seen in Waldenstrom's macroglobulinemia[6], there have been no reports of increased IOP in polycythemia.

It is not the intention of the author to imply that all of these factors are irrefutable causes of increased IOP, or definite predictors of the likelihood of a transition from ocular hypertension to chronic simple glaucoma. Many of the studies mentioned above showed associations which were definitely at the level of statistical significance. This, however, does not prove that one observation was the cause of another. Some of the epidemiological factors might indeed be causal, while others might be simply spurious associations. An attempt has been made to point out the controversies and inconsistencies where they existed.

In practice, some individuals who have been found to have increased IOP will go on to develop the cupping and optic atrophy of glaucoma, although most will not. Nevertheless some physicians regard the situation of IOP as early primary open-angle glaucoma and initiate treatment. Others feel that treatment is not indicated, as only 5-10% of these patients with IOP between 20 and 30 mm Hg will go on to develop frank glaucoma[2].

Chisholm feels that the actual IOP at the time of the diagnosis of ocular hypertension, sex or a family history of glaucoma are poor predictors of the likelihood of making the transition from ocular hypertension to glaucoma. The absence of hypermetropia, on the other hand, is viewed as a good predictor, as is the "subnormal" visual field, or an age of over 60 years. Chisholm is currently concerned with the unjustified use of antiglaucoma medication by many physicians in their excessive eagerness to treat the patient with a high IOP. His studies have shown that patients with ocular hypertension using antiglaucoma medication develop glaucoma significantly sooner than ocular hypertensive controls.[2] (One may argue, however, that the eye was indeed glaucomatous from the start, and that the central scotoma was missed).

Summary

In summary, there are many epidemiologic factors which are associated with ocular hypertension, including ocular factors (refractive error, axial eye length), age, sex, systolic blood pressure, metabolic disease (diabetes, obesity, macroglobulinemia) and steroid use.

However, since ocular hypertension is still a controversial matter as far as glaucoma development is concerned, these epidemiological factors become moot points. Therefore, one turns to the basic medical edict of treating all patients as individuals (taking epidemiological factors into account secondarily). □

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Malignant Pleural Effusions And The Use of Talc Poudrage

George Vincent 8T3

Thirty-six patients with recurrent malignant pleural effusions treated with talc poudrage were studied. The two most common primary carcinomas associated with malignant effusions were of lung and breast. Dyspnea was the predominant presenting symptom. Sixty-five percent of malignant effusions were found to be serosanguinous. The combination of effusion cytology and pleural biopsy had a sensitivity of 94% for the diagnosis of malignant effusions. Seventy-five percent of patients treated with talc poudrage did not require further treatment. Radiological determination of post-talc poudrage effusion was found to be unreliable. Thirty-four percent of patients were alive 6 months after talc poudrage.

Pleural effusion is a complication of malignant neoplastic disease. It may lead to premature death from acute respiratory failure, or its chronic symptomatology may seriously debilitate the patient.[1 3 8]

How a malignancy produces an effusion is not precisely known. Many theories have been suggested [6 7 11] —explanations which require an understanding of fluid hydrodynamics through the pleural space. Fluid movement follows Starling's principles. Under a high systemic hydrostatic pressure, fluid leaves the capillaries of the parietal pleura and enters the pleural space. Fluid then passes through the visceral pleura, primarily by being drawn directly into the capillaries by oncotic pressure, and also by entering the visceral lymphatics.[3]

Pleural fluid movement is thus regulated by 5 forces:

1) systemic hydrostatic pressure
2) pulmonic hydrostatic pressure
3) oncotic pressure
4) capillary permeability
5) lymphatic drainage

One theory suggests that malignant cells can obstruct the subpleural, parenchymal or hilar lymphatics, causing impaired fluid absorption. Another theory contends that, by altering the capillary permeability, the malignancy substantially increases the amount of pleural fluid beyond the lung's capacity to absorb it.

Treatment By Talc Poudrage

Isolated pleural effusions are commonly treated by closed thoracotomy drainage, but this method is not suitable for recurrent effusions. A more permanent and palliative treatment is pleurodesis — fusion of the parietal and visceral pleurae, which thus obliterates any space for fluid accumulation. Pleurodesis may be difficult, and many methods have enjoyed limited success.[3 8] One of the better methods consists of insufflating talc powder (an insoluble compound of magnesium and aluminum silicates) into the pleural space. N. Bethune (McGill University, 1935) initially developed this technique (as a means of obliterating the pleural space) as a preliminary procedure for lobectomy during open ventilation; however, its use soon caught on for the treatment of effusions.[4]

The pleurodesis produced by talc results from an adhesive, obstructive pleuritis[6] without excessive granulomatous formation.[5] For proper pleural symphysis, it is essential that the two pleurae be in apposition for the first two or three days following poudrage[1]. Both pleurae must also be homogenously coated with the talc, which is accomplished during surgery by having the patient breathe spontaneously, drawing talc into the pleural space on inspiration.

The insufflated talc immediately evokes an inflammatory reaction which restricts inspiration and expiration, thus temporarily decreasing lung volume. A subsequent return to normal occurs within 2 months in 90% of patients.[9] Due to the generally grave prognosis of the patients with malignancy, the long-term effects of talc poudrage cannot be ascertained.

Talc poudrage is considered a palliative procedure used only to improve the quality of life. It is indicated when the following conditions have been met:

1) the effusion is identified as malignant;
2) relief of symptoms follows thoracentesis;
3) the lung is fully expandable after thoracentesis;
4) pleural effusions are recurrent;
5) the patient is deemed to have a relatively long term life expectancy.[2]

The Surgical Procedure

Under general anaesthesia the patient is intubated, and is positioned so that the side containing the effusion is superior. The patient ventilates spontaneously throughout the entire procedure. Two trochars are inserted into the pleural space — one in the 7th or 8th intercostal

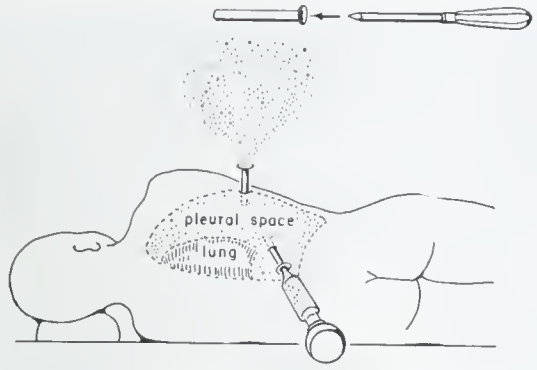

Figure 1: Diagrammatic illustration of a talc poudrage using a 2-trochar technique. (Reprinted with permission from Pearson and MacGregor, 1966)[11]

space posterolaterally, and the other in the 2nd intercostal space at the midclavicular line, Fig. 1.

The lung collapses spontaneously, and the effusion is drained through one of the trochars. While the patient inspires, talc powder is insufflated through each trochar, care being taken to ensure homogenous coating of both pleurae. Chest tubes are inserted through the wounds, and once secured to the skin, are connected to an underwater seal and a suction device. The chest tubes are removed on the 4th or 5th post-operative day.

Retrospective Clinical Review

The data in this study were collected from 36 patients treated with talc poudrage for malignant pleural effusions, between 1973 and 1980 at Mount Sinai Hospital, Toronto.

Table 1 shows the correlation between the sites of the primary tumor and the characteristics of the malignant effusions. Breast and lung carcinoma accounted for most of the primary tumor sites. Adenocarcinoma was the most common neoplastic cell type (70%). The remainder (30%) consisted of lymphoma, mesothelioma, fibrosarcoma and cells of unknown origin. The data also indicate that pleural effusions occurred 3 times more often in females than in males. The large number of females treated for breast cancer accounted for this difference.

From the study two groups of patients were distinguished: those in whom an effusion followed the diagnosis of primary carcinoma, and those in whom it preceded the diagnosis. The average interval between the diagnosis of primary tumor and the first effusion was 61 months; between the first effusion and the diagnosis, it was 0.3 months. Effusion appeared, on the average, 53.5 months after the diagnosis of primary breast carcinoma.

The commonest presenting symptom of pleural effusion in these patients was dyspnea (86%), followed by cough (usually non-productive) in 38%, and chest pain in 11%. Three percent were asymptomatic.

The combination of effusion cytology and pleural biopsy histology proved to be the most effective diagnostic method, having a combined sensitivity of 94%. Sixty-five percent of the effusions obtained were serosanguineous.

In 51% of the treated cases, the surgical routine involved bronchoscopy, pleuroscopy with pleural biopsy, and talc poudrage (procedure as described). The talc poudrage was, however, done under local anaesthesia in one patient: dissolved in saline, the talc was injected into a previously-positioned chest tube. Right talc poudrage was performed twice as often as left.

Post-operatively, 16 of the 36 patients had a subsequent effusion identified by chest x-ray. For this group, an average of 3.8 months (median, 1.3 months) elapsed between surgery and the effusion. Nine of these patients later underwent thoracentesis. Documentation was unavailable for the other patients; it is not known whether they remained without effusion, or had an unreported effusion. Thirty-four percent of the talc poudrage treated patients lived for 6 months or longer afterwards.

Figures 2a and 2b demonstrate the radiographic difference talc poudrage made for one patient.

Table 1: Correlation between site of primary tumors and the characteristics of the effusions treated by talc poudrage.

1° Tumor	Number of patients	Frequency (%)	Average age of occurence of effusion[b] (yrs)	Frequency of side on which effusion occurred (%)		Predominant cell type
				Right	Left	
Breast	17	47	60 (48-78)	67	33	adenocarcinoma
Lung	7	19	69 (50-94)	43	57	adenocarcinoma
Other[a]	12	34	62 (20-81)	75	25	—

a - includes cancer of kidney, stomach, thyroid, mesothelium, bone, lymphoma and unknown primaries.
b - values in brackets refer to range of values

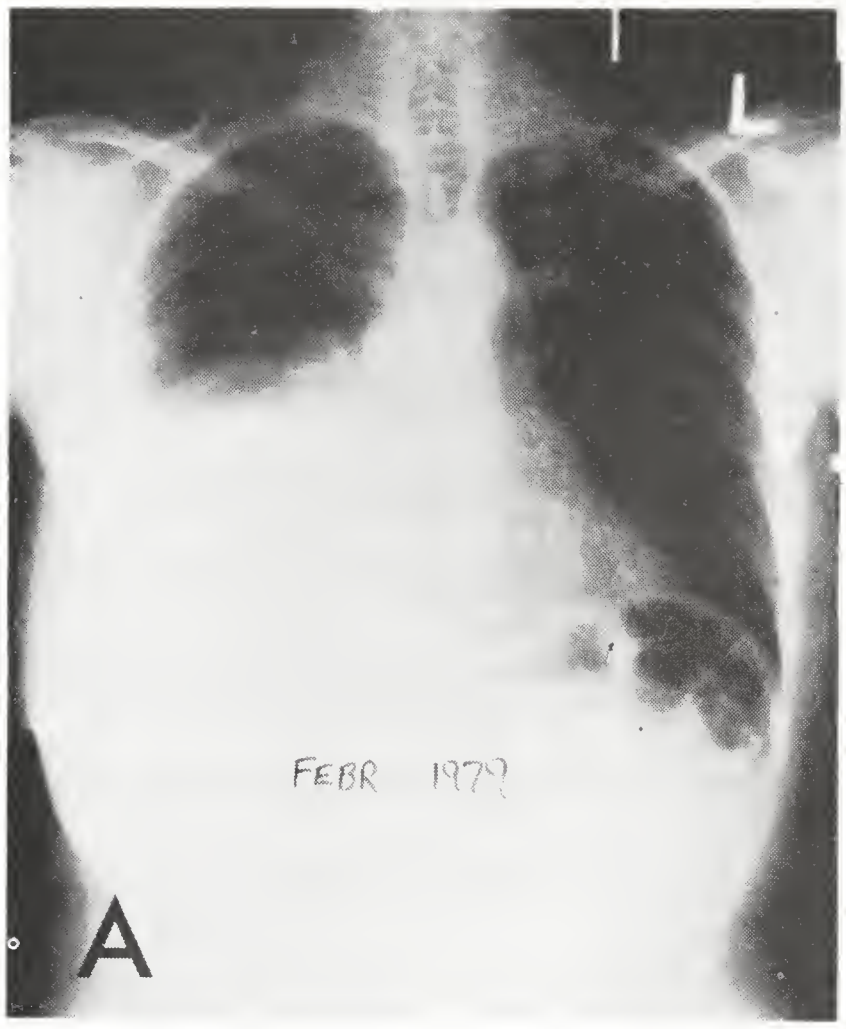

Figure 2a: Chest radiograph of a patient showing a right pleural effusion, 9 years after left radical mastectomy for breast cancer.

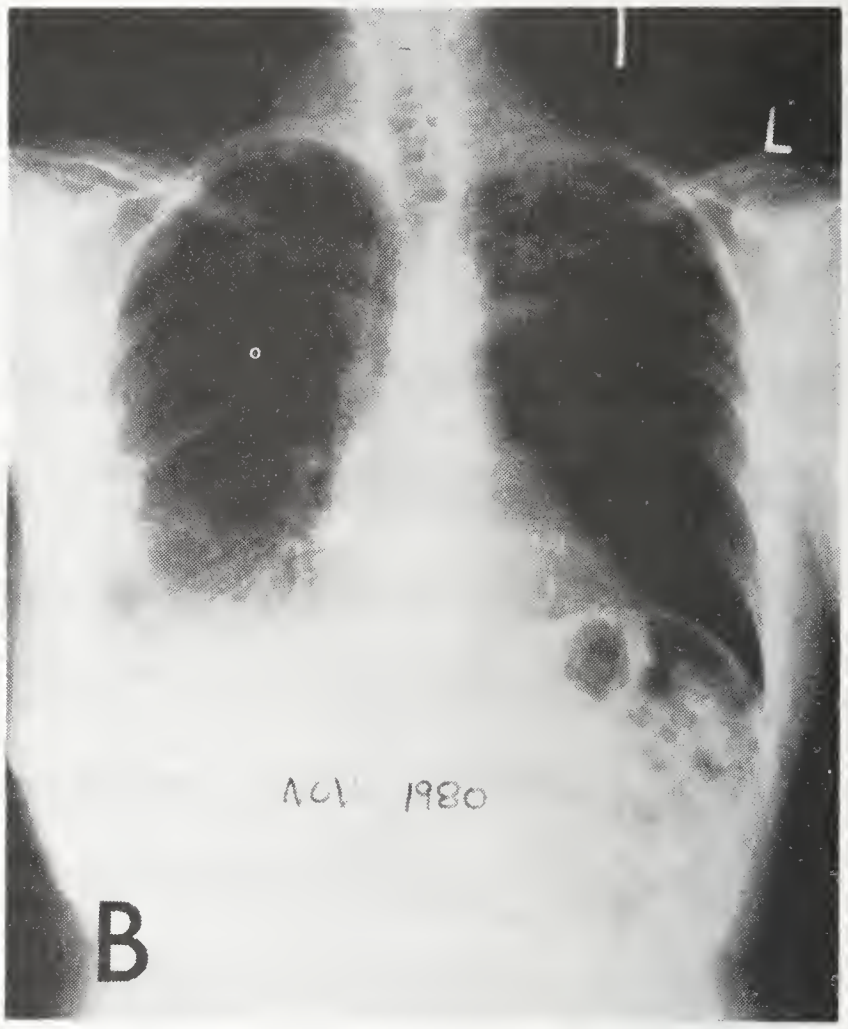

Figure 2b: Same patient 21 months after right talc poudrage.

Discussion

The high frequency of malignant pleural effusions produced by breast and lung cancer, as ascertained in this study agrees with the findings of other investigators[1 2 10 11]. Ultmann has suggested that 50% of patients with breast cancer ultimately develop pleural effusions.[12] Pearson and MacGregor have put forth a plausible explanation: malignant cells from a breast primary, by travelling through the mediastinal nodes and along the bronchovascular lymphatics, can obstruct the subpleural lymphatics, thus causing the effusion.[11] If this explanation is indeed correct, the present study has shown the time necessary for lymphatic obstruction (leading to effusion) to be an average of 53.5 months after the diagnosis of breast carcinoma.

This study, and that of Adler and Rappole[1], both demonstrate the predominance of dyspnea (86-90%) as the presenting symptom. The dyspnea is apparently caused by compression of the underlying lung by the effusion, and by a mediastinal shift compromising function of the contralateral lung.[7 11]

Leuallen reports that the majority of malignant effusions are bloody[10]; this agrees with the 65% figure obtained in this study. Others have also documented the effectiveness of combined effusion cytology and pleural biopsy as a means of diagnosis.[3]

A literature search of the effectiveness of talc poudrage turned up the following: two studies reported prevention of recurrent effusions in 100% of cases[1 7], while three others reported figures in excess of 75%.[5 6 11] The proportion in this study is thus comparable (75%). After talc poudrage, at least 44% of patients had subsequent effusions identified radiologically, but in many, thoracentesis did not confirm the effusion. This can be explained by the difficulty in distinguishing on x-ray a true effusion from pleural thickening secondary to the effects of talc. Recurrent effusions are thus best identified by clinical assessment, radiologic suggestion, and ultimately, thoracentesis. □

Acknowledgement

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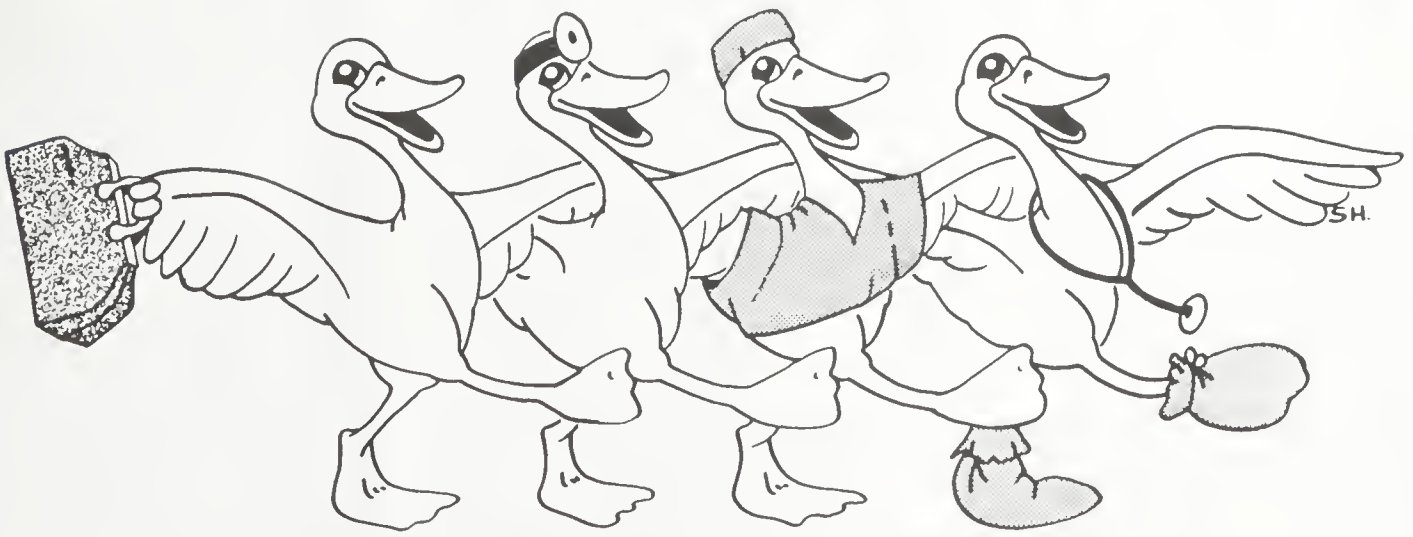

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Phlebotomy For Cyanotic Congenital Heart Disease

Elliott Weiss 8T2

The secondary polycythemia of cyanotic congenital heart disease can adversely affect exercise tolerance as well as disrupt the coagulation process. By performing phlebotomy (a procedure equivalent to donating blood), the red cell concentration can be reduced to a level more tolerable to the body. The complications of this disease are thus reduced while the quality of life of these patients is significantly improved.

Of the wide variety of congenital diseases of the cardiovascular system, those that produce a state of central cyanosis can be the most serious. In cases of long-standing tetralogy of Fallot and ventricular septal defects, the development of the Eisenmenger complex can cause much of the blood that enters the right ventricle to be shunted to the left (compared to the acyanotic condition in which the shunting is left to right). With the increased volume and pressure in the right ventricle, pulmonary hyperplasia occurs secondary to pulmonary hypertension, thus limiting blood flow through the lungs. This re-routing of blood has further effects on the body, one of the most important being secondary polycythemia (an overproduction of red blood cells).

The secondary polycythemia in cyanotic congenital heart disease (CCHD) is associated with an increased incidence of hematological abnormalities.[1] [4] Post-operative bleeding, cerebrovascular accidents and consumptive coagulopathies are more common in cases of CCHD.[3] [5] [10] Surgical treatment of these patients early in life may correct their hemodynamic disturbances but later once the secondary changes of pulmonary hyperplasia have occurred, surgery may adversely affect the patient by restricting pulmonary blood flow. Medical management of CCHD, while not correcting the primary disturbance, can improve the quality of life as well as reduce the complications associated with this disease.

Prophylactic medical management is the key to CCHD where surgery is contraindicated. Obviously, by preventing or reducing complications of this disorder, mortality and morbidity can be reduced. However, the factor that is most restrictive in the patient's life is the cyanosis associated with exertion. The classical case is that of the patient who, following physical activity, assumes a squatting position in an attempt to relieve his shortness of breath.

Yet polycythemia, a physiological attempt by the body to increase the oxygen-carrying capacity of blood can be self-defeating. Hematocrits of 75% and hemoglobins of 25 mg/dl or more can occur.[11] [12] With red cell levels this high, viscosity and shear forces of blood through the peripheral and pulmonary vasculature are increased significantly. This places further strain on the heart, which is already coping with a larger than normal volume of blood—some of which is pumped inefficiently due to the effect of shunting.

The use of phlebotomy, a procedure equivalent to donating blood, can be effective treatment here.[11] [12] By repeatedly withdrawing small quantities of blood (up to 500 cc) over an extended period of time, the hemoglobin and hematocrit can be reduced to levels more tolerable to the body. Still, there are interesting and fundamental effects that phlebotomy can have on these patients. Thus a discussion of both the cardiovascular and hematological changes with phlebotomy in CCHD is warranted.

Cardiovascular Effects of Phlebotomy

By reducing blood volume and decreasing the quantity of red cells in blood, viscosity and shear forces are reduced in the vascular system. It has been found that a net decrease in left-to-right shunting occurs following phlebotomy.[11] This can be explained by a steeper drop in peripheral resistance than in the pulmonary component. In addition, venous return to the heart increases. The net effect is to augment systematic oxygen saturation with little change in "effective pulmonary flow".[11] Thus, flow rates and oxygen delivery to the tissues increase.

Cardiac output increases, yet cardiac oxygen consumption is affected little, if at all.[12] [13] Clinically, exercise tolerance increases even if the patient's systemic oxygen saturation rises only slightly. Studies have also shown that polycythemia in CCHD is due to an increase in red cell volume while the plasma component of blood remains within normal limits.[13] [14] [15] The cardiovascular system is stressed more by an increase in viscosity and red cell volume than a rise in the plasma component.[16] Still, blood volumes as high as 11 liters have been reported.[17] Phlebotomy, then, reduces the considerable strain on

the heart caused by the increased viscosity and total blood volume.

Hematological Effects of Phlebotomy

Disorders of the blood have been recognized in CCHD for many years. In 1911, a cyanotic patient with pulmonary stenosis was noted to have a "tendency to epistaxis".[18] Yet disorders of the coagulation system may not be unique to the cyanosed with congential heart disease. In acyanotic patients there is "some laboratory evidence of a pre-existing diathesis" and abnormal levels of the components of coagulation have been found.[3] [19] [20] Thus hematological changes can occur in congential heart disease independent of oxygen saturation.

With the additional stress of polycythemia and reduced oxygen levels, the platelet count and various coagulation factors are reduced further. This may be explained by a decrease in blood oxygen which lowers platelet half-life.[1] [4] Hypoxia of bone marrow and hepatocytes may also be important here.[19] [20]

These alterations in the hematological status can have serious consequences for the patient. The increased viscosity and coagulability of blood due to polycythemia may be responsible for the increased incidence of cerebrovascular accidents.[7] [8] Another disease whose association with CCHD is controversial is disseminated intravascular coagulation. This will be discussed in a subsequent section.

Using phlebotomy to lower red cell levels will not completely normalize the platelet count nor return the components of coagulation to optimal levels. However, phlebotomy can evoke a rise in platelets from 50 x 10^6/L to 150 x 10^6/L which is significant and possibly life-saving. While the hemostatic complications of CCHD may be uncommon, predisposing factors are lessened, as shown by partial thromboplastin, prothrombin, and clotting times which approach normal levels. Phlebotomy, then, can be considered both therapeutic as well as prophylactic in nature.

The Diagnosis of Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) associated with CCHD has been a diagnosis of controversy for over a decade. Mucosal bleeding, generalized ecchymosis and purpuric lesions may be present, as well as other specific organ damage. The laboratory diagnosis requires thrombocytopenia, raised prothrombin and partial thromboplastin times as well as the presence of fibrin degradation products in the blood. Treatment of choice is heparin. Various studies over the years have suggested that a low-grade consumptive coagulopathy (or DIC) may exist in some patients with CCHD.[19] [20] [21] However, hypoxia of the liver and bone marrow, along with venous stasis, have also been offered as explanations for these hematological abnormalities.[19] [20] Others have found no improvement in such patients treated with heparin.[3] [22] [23] [24]

Primary fibrinolysis has been considered in the differential diagnosis of DIC.[25] To confirm this diagnosis, a very rapid euglobin clot lysis time with little or no thrombocytopenia must be present (in the patient without CCHD). Diagnosis may be more difficult in CCHD since a degree of thrombocytopenia can be a consequence of this condition. The treatment here is e-amino-caproic acid. In any case, the diagnosis of DIC in a patient with CCHD requires further investigation and follow-up—especially when the use of heparin is considered for patients with reduced levels of coagulation factors.

Phlebotomy prevents or reduces the hypercoagulable state of the blood, while low oxygen levels may be somehow involved in a low-grade consumptive coagulopathy. While not an ideal method of treating an acute DIC, phlebotomy may prevent or slow the processes leading to a subsequent attack, and is thus of therapeutic value.

The Clinical Decision

The decision to perform phlebotomies is primarily a clinical one. The symptoms of secondary polycythemia in CCHD varies from patient to patient—he may complain of headaches, and be irritable, anorexic and dyspneic. The patient with a hematocrit of 75% and who also suffers frequent blue-black spells would likely benefit from phlebotomy, while another patient may cope quite well with the same red cell level.

Maintenance of a hematocrit of 55 to 60% has been found to achieve good results in the general management of these cases[11] [12] Because the removal of large quantities of blood increases the risk of vascular collapse, a number of phlebotomies removing smaller quantities of blood is preferred. It is also important to ensure that adequate stores of iron, vitamin B^{12} and folate exist.[9] [14] In fact, if the hematocrit fails to rise in time, it most commonly suggests a folate deficiency. Normally, phlebotomies will need to be repeated, possibly on an annual basis, as the persistent cyanosis continues to stimulate excess red cell production. The risks of the procedure include vascular collapse, but under close supervision, the procedure is both safe and effective.

In the surgical application, phlebotomy may improve the patient's cardiovascular status and has been shown to reduce post-operative hemorrhages by up to 110% (with an optimal hematocrit of 55 to 60%).[26] Furthermore, the blood removed could be used for management during and after the operation, as required.

Conclusion

The medical management of patients with cyanotic congenital heart disease may include the use of phlebotomy when performed conservatively. The quality of life for these patients can be improved significantly by increasing exercise tolerance. As well, the reduced hematocrit diminishes stresses on the cardiovascular and coagulation systems. The procedure is both palliative and preventative in nature, and should be considered in cases of CCHD. □

(continued on page 103)

Calcium Antagonists

Dominic Raco 8T1

Within the last year, verapamil, the prototype calcium antagonist, has come on the market in Canada. Here, it is only available in the intravenous form and licensed solely as a cardiac antiarrhythmic. In Europe, this drug has many years of clinical experience (in the oral and intravenous form) as the drug of choice in the treatment of several arrhythmias, and is also used in ischemic heart disease and hypertension.

Introduced in 1962, verapamil was thought to be a beta-receptor blocker, but was later found to have a novel mechanism in the selective inhibition of calcium transport. Three other calcium antagonists are currently being explored - nifedipine, diltiazem and D-600. The objective of this paper is to provide an overview of this promising family of new agents which is gaining much prominence in cardiovascular therapeutics.

The well-recognized cardiac action potential is illustrated in Figure 1. Besides the rapid Na + influx and K + outflux producing depolarization and repolarization, there is a slow transmembrane calcium current across the sarcolemma which produces the plateau phase of the action potential. A small quantity of extracellular calcium enters the cell through special channels in the sarcolemma and triggers the release of large amounts of calcium from the internal stores in the sarcoplasmic reticulum. When the available intracellular calcium concentration exceeds 10^{-7} M, muscular contraction occurs. Smooth, like cardiac muscle, requires this extracellular Ca^{+2} trigger and similarly has a long action potential. Since this extracellular initiation is not required in skeletal muscle, there is no plateau phase in its action potential.

It is readily apparent that calcium is central to the electrical-mechanical coupling of cardiac function. An even more critical role is played by calcium in the sinus and AV nodal cells, where it is calcium influx that produces the slow phase 4 depolarization.

Mechanism of Action of Calcium Antagonists

We now realize that there are 3 ways in which Ca^{+2} can penetrate the sarcolemma. Besides the slow-channel Ca^{+2} transport that produces the plateau phase of the action potential, there is also passive Ca^{+2} transport and an active Ca^{+2} -2Na + exchange mechanism across the cell membrane. The loosely classified 'calcium antagonists' actually block the slow calcium channels in the myocardial sarcolemma, thus inhibiting the inward transport of Ca^{+2} during the plateau phase in the myocardial cells, and phase 4 in the specialized nodal cells. It has been proposed that there are different types of slow Ca^{+2} channels, and various calcium antagonists are felt to selectively block some channels more than others (analogous to alpha and beta-adrenergic blockers). This model can explain why nifedipine is 10-100X more potent than verapamil as a smooth muscle relaxant while it has no effect on the cardiac conducting tissue.

The effects of this slow-channel calcium-influx inhibition on the heart are illustrated in Figure 2.

Figure 1

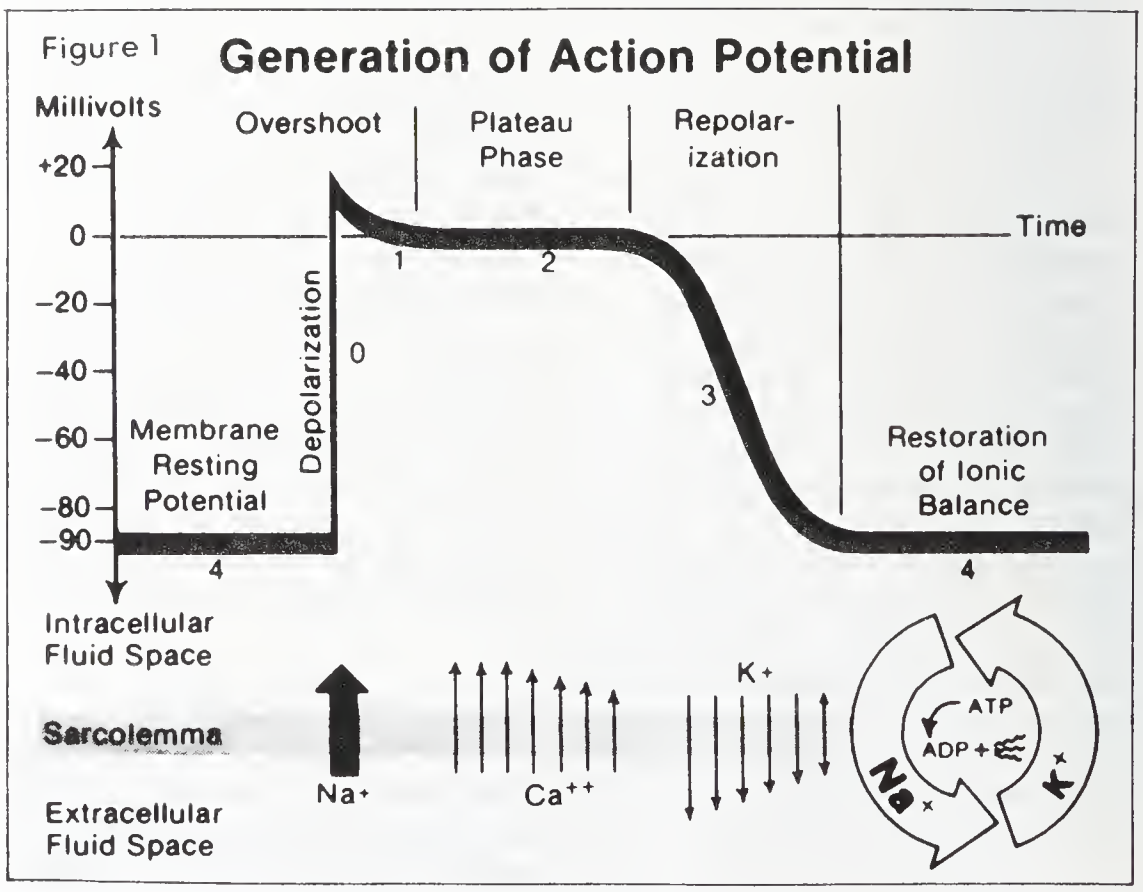
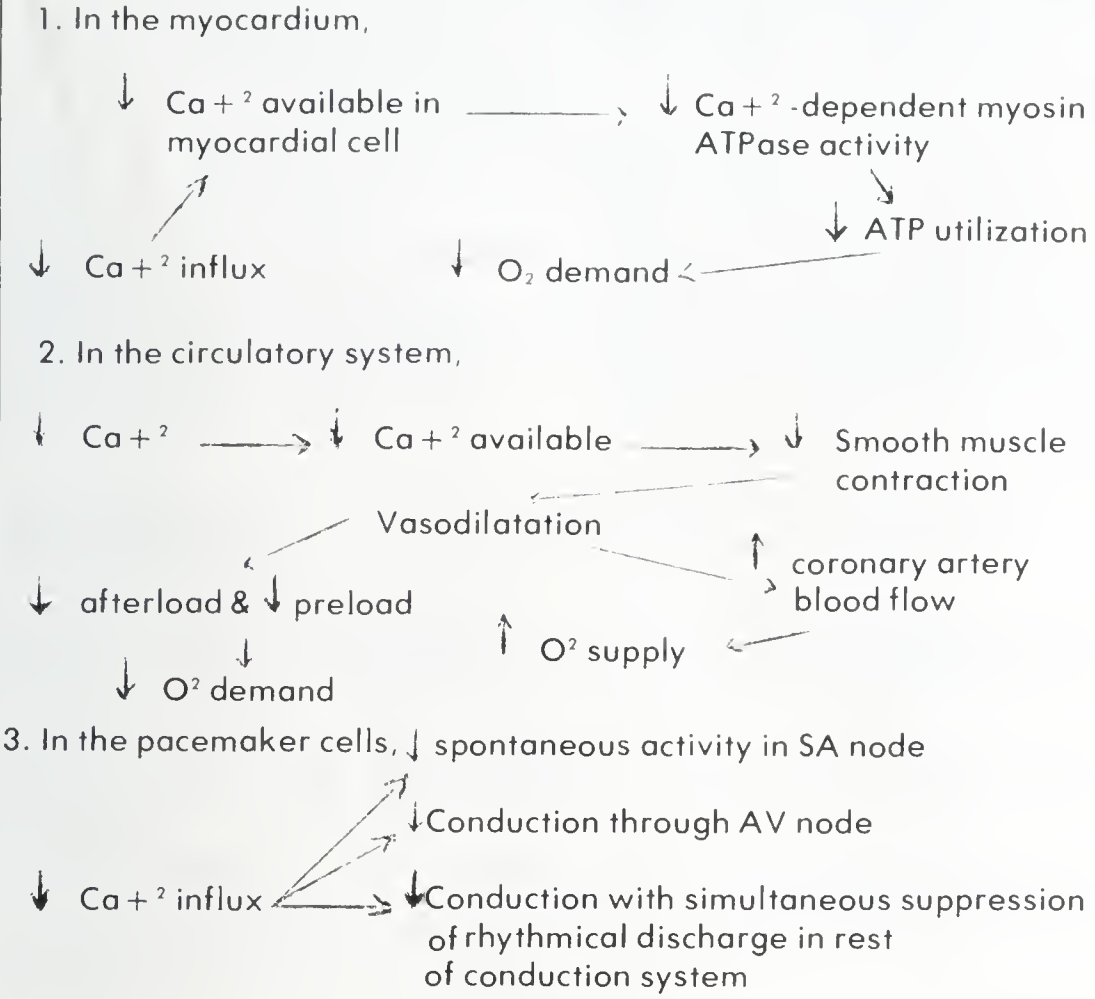


Figure 2


1. In the myocardium,
↓ Ca + ² available in myocardial cell
↓ Ca + ² -dependent myosin ATPase activity
↓ ATP utilization
↓ Ca + ² influx
↓ O₂ demand
2. In the circulatory system,
↓ Ca + ²
↓ Ca + ² available
↓ Smooth muscle contraction
Vasodilatation
↑ coronary artery blood flow
↓ afterload & ↓ preload
↑ O² supply
↓ O² demand
3. In the pacemaker cells, ↓ spontaneous activity in SA node
↓ Conduction through AV node
↓ Ca + ² influx
↓ Conduction with simultaneous suppression of rhythmical discharge in rest of conduction system

Verapamil thus decreases cardiac oxygen demand by limiting myocardial inotropy, and by systemic vasodilatation which decreases preload and afterload. The most marked decrease in vascular resistance occurs in the coronary arteries, and this serves to increase the myocardial oxygen supply. The electrical alterations in the nodal system, combined with the more advantageous supply-demand environment created in the myocardium, result in the antiarrhythmic activity of verapamil. Nifedipine and Diltiazem have no action on the pacemaker cells, making them of no use as antiarrhythmics.

Pharmacology of Verapamil

The prototype calcium antagonist, verapamil, is a synthetic papaverine derivative and a weak local anaesthetic.

The inhibition of calcium influx produced by verapamil and the resultant impairment of muscular contraction is found not only in heart muscle, but also in the smooth muscle of the uterus, intestines and arteries. Its antiarrhythmic effect is mainly at the AV node. In contrast to other antiarrhythmics, verapamil does not affect the duration of the action potential and the rate of conduction in the atria and ventricles.

The pharmacokinetics of verapamil have not been well established and those of other calcium antagonists are very scanty.

80-90% of oral verapamil is rapidly absorbed by the intestinal tract but, because of significant first-pass hepatic metabolism, there is only 10-22% bioavailability. Consequently, the required oral dose is 8-10 times greater than the intravenous dose. Approximately one hour after an oral dose, maximal levels are reached in the plasma where the drug in 90% protein-bound. Verapamil is metabolized to numerous hepatic metabolites—not all of which are known and some of which are active. These are excreted in the urine and the bile. The elimination half-life of the drug is 3-10 hours and none is found in the plasma 48 hours after an oral dose.

Toxicology testing in animals has shown that very high levels of verapamil are tolerated (oral LD^{50} is in the range of 150mg/kg). The drug has not been found to be teratogenic in animals.

Indications

A) Ischemic Heart Disease

A multitude of studies (Livesley, 1973; Krikler, 1974; Singh, 1975; Andreasen, 1975) indicate that verapamil reduces the frequency and severity of angina pectoris. It is as effective as beta-blockers in the treatment of angina, and may have a particular advantage over beta-blockers in angina caused by coronary artery spasm (Prinzmetal's angina). Verapamil has been shown to reduce nitroglycerine intake and to decrease the ST segment of verapamil on an ischemic heart mentioned earlier in this paper (decreased O_2 demand and increased O_2 supply) seem to hold true in practice, but because of reflexes in the intact cardiovascular system, inotropy and blood pressure are maintained.

Animal experiments (Naylor, 1976) have shown that verapamil pretreatment will protect mammalian heart muscle against the deleterious effects of hypoxia and eschemia, as well as limiting the size of a myocardial infarction. On the basis of this evidence, verapamil is used in Europe for the prophylaxis and follow-up treatment of myocardial infarction.

B) Arrhythmias

Verapamil has been found to be as effective as any other drug used today in the treatment of supraventricular tachyarrhythmias (Table 1). Intravenous verapamil, by its influence on the calcium-dependent phase of the nodal cell action potential, has two main effects on cardiac rhythm (Figure 3):

1. a marked slowing of ventricular rate; and,
2. a regularization of the ventricular rhythm.

Although several drugs (such as digoxin) will slow the ventricular rate in atrial fibrillation, they do not have the property of regularization of the ventricular rhythm. Verapamil has been found to be most useful before cardioversion, where it can slow and regularize ventricular rates, and after cardioversion, to maintain sinus rhythm. Verapamil may have a synergistic effect with quinidine in

treating chronic atrial fibrillation.

Supraventricular tachyarrhythmias are generally a result of a re-entry pathway which includes either the sinus or the AV node. The inhibitory effect of verapamil on these nodal centres results in the blocking of the re-entry circuit, thus terminating the arrhythmias. The other two mechanisms proposed for arrhythmias (increased automaticity and after-depolarization) will also be beneficially influenced by verapamil.

The only important supraventricular tachyarrhythmias which are not benefited by verapamil are found in association with accessory pathways (the pre-excitation syndromes, of which Wolff-Parkinson-White is the most common) and sick-sinus syndrome. Verapamil has little effect on anomalous pathways. If given for a tachycardia in association with sick-sinus-node syndrome, it may cause severe bradycardia or asystole because of its inhibitory effect on the compromised sinus node.

Although verapamil will reduce the frequency of ventricular extrasystoles, especially in association with cardia ischemia and surgery, there are several other agents that are generally more effective for ventricular arrhythmias. Verapamil will probably not become a first-line drug in these situations, but may, because of its unique calcium-antagonism property, become useful for isolated ventricular arrhythmias.

Most of the investigative and clinical antiarrhythmic use has been with intravenous verapamil. Oral verapamil as a prophylactic treatment of different arrhythmias is presently under investigation, but it is felt that the main antiarrhythmic thrust of this drug will be in the intravenous form.

C) Hypertension

The vasodilatory effect of verapamil and its possible indication in hypertension are currently being explored. Several studies have shown it to reduce systolic and diastolic pressures without significant hypotensive side effects (Schmitt, 1967; Brittinger, 1970). There are no long-term studies with oral verapamil as an anti-hypertensive, and it would seem that with the multitude of anti-hypertensives already on the market, little would be gained by using verapamil in this respect. Intravenous verapamil may be of use in hypertensive crises (Brittinger, 1970), and may be advantageous over other drugs because of its safety in renal insufficiency.

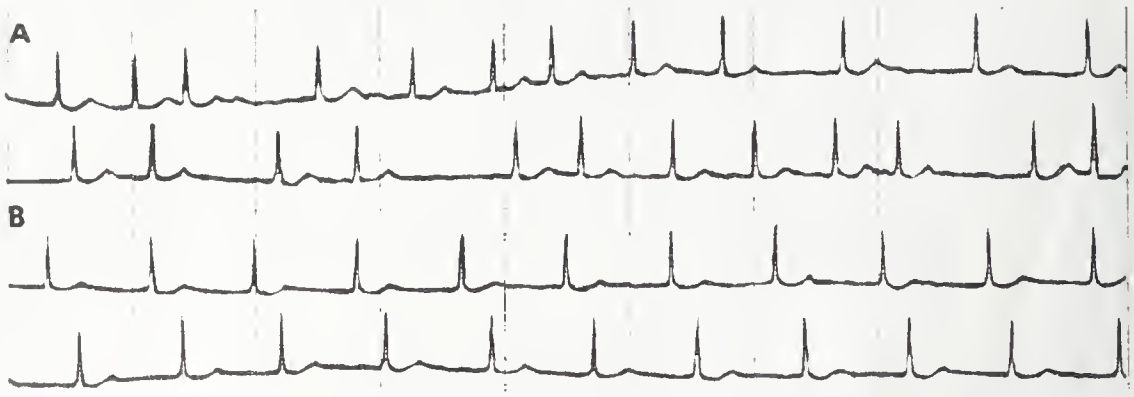


Fig. 3 Atrial fibrillation with rapid ventricular response. **A:** Before administration of Isoptin. **B:** 5 minutes after intravenous injection of 10 mg Isoptin (continuous recording of Standard Lead II).

Table 1

Arrhythmias	Positive Result	% Positive Results	
		B	S
atrial fibrillation with rapid ventricular response	slowing or conversion to sinus rhythm	95%	96.5%
atrial flutter with rapid ventricular response	slowing or conversion to sinus rhythm	95.5%	100%
paroxysmal supra-ventricular tachycardia	conversion to sinus rhythm	100%	100%
ventricular extra-systoles	eliminates extra-systoles	77.7%	50%

B Bender, Arznein-Forsch. 20, 1310-1316 (1970); 152 patients.
S Schamroth et al, Brit. Med. J., 1, 660-662 (1972); 181 patients.

D) Other Uses

Among the other possible cardiovascular indications for the calcium antagonists, idiopathic hypertrophic subaortic stenosis is the latest established beneficiary of verapamil.

The novel mechanism of action of these drugs and their effect on non-cardiac human physiology are in the infancy stage of exploration. Weidinger and Wiest (1971) have shown verapamil to be useful in threatened abortion or premature labour, as it inhibits uterine muscle contraction. There is anecdotal evidence for use in intermittent claudication and in vasospastic diseases (such as Raynaud's phenomenon).

In research, calcium antagonists have become a vital tool in exploring calcium physiology.

Side Effects

The incidence of severe reactions requiring discontinuation is reported by Knoll Pharmaceutical Company to be 1% lower than other cardiovascular drugs used for similar indications. The side-effects consist mainly of hypotension, blocking of the AV node and heart failure. Unlike beta-blockers, verapamil will not produce bronchospasm and can be used freely in patients with C.O.L.D.

Contraindications

There are no contraindications to continuous long-term oral verapamil treatment, but there are several in

association with intravenous use—they are:
1) cardiogenic shock;
2) the acute stage of MI(with the possible exception of concurrent tachy-arrhythmia treatment);
3) complete AV block; and,
4) overt heart failure.

The relative contraindications for intravenous use are:
1) partial AV block and LBBB;
2) marked bradycardia; and,
3) hypotension.

Precautions

The concurrent use of verapamil and certain other drugs may have undesired effects and should be avoided. Verapamil and beta-blockers synergistically cause depression of the myocardium, and of the SA and AV nodes. Disopyramide phosphate is contraindicated 48 hours before and after verapamil. Caution should also be used when verapamil is combined with other drugs that have high plasma protein binding (such as Warfarin) as displacement from the proteins may alter the bioavailability of these drugs.

As previously mentioned, verapamil has a variable effect in sick sinus node syndrome and may cause asystole.

Finally, heart failure should be controlled with cardiac glycosides before verapamil is introduced.

Dosage (Verapamil)

For the treatment ot angina pectoris, tachyarrhythmias and hypertensive crises, 5-10mg. of verapamil may be injected intravenously, slowly over 15-30 seconds. During the bolus injection, ECG and frequent blood pressure monitoring is advised. The dose may be repeated 10 minutes later. Alternatively, an intravenous infusion of verapamil in any of the common solvents may be given at a rate of 5-10mg/hour up to a total dose of 100mg/day.

Oral therapy is given for the prophylaxis of angina pectoris and supraventricular tachycardia, for the long-term treatment of chronic coronary insufficiency, and for the prophylaxis and follow-up treatment of MI. An initial oral dose of 40 to 80mg t.i.d. can be increased to 240mg t.i.d. over 2 to 3 days.

Summary

As mentioned previously, the broad clinical use of verapamil is narrowed in Canada by licensing procedures. Thus far in Canada, it has been licensed for use as an intravenous antiarrhythmic and is marketed by Pentagone Laboratories under the trade name Isoptin. We will undoubtedly see the oral form and wider spectrum of uses licensed in Canada in the near future.

We have discussed calcium antagonists, their mechanism of action and clinical utilization. This new family of drugs has provided a new weapon in the armamentarium of cardiovascular pharmaceuticals. Like all new drugs, only the test of widespread clinical utilization will elicit the actual benefit of verapamil for our patients. □

Acknowledgement

The author would like to thank Dr. P.H. Tanser for his kind help and supervision. He would also like to acknowledge Pentagone Laboratories, affiliates of Knoll Pharmaceutical Company, West Germany, who provided references.

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Spontaneous Osteonecrosis Of The Knee

Brian Alpert 8T2
Emil Orsini 8T3

Spontaneous osteonecrosis of the knee (S.O.N.K.) may be one of the initiating lesions in the development of idiopathic osteoarthritis. Radionuclide bone scans are the key to the early diagnosis and treatment of S.O.N.K. This article will, first, review the causes of osteonecrosis in the knee and then, present the results of a study on S.O.N.K. illustrating the clinical, radiological, and bone scan findings.

Osteonecrosis is defined as the death of bone cells.[7] This phenomenon has been well described as occurring in the femoral head but it is only since 1966 that it has been documented in the femoral condyles.[2] In 1980, osteonecrosis of the medial tibial plateau was described in the literature.[12 18]

The clinical significance of osteonecrosis, in the usual epiphyseal location, is related to the structural changes that it induces in the subchondral bone and articular cartilage on both sides of the joint.[7] These structural changes alter the biomechanics of the joint and often lead to the development or progression of osteoarthritis (OA) and joint destruction. It should be noted that radiological evidence of OA can be found in 85% of the population over the age of 70[10] and that the knee is the joint most commonly affected.[1] Thus, osteonecrosis of the knee, which has been implicated in the development and progression of OA, has great clinical importance to all physicians.

This paper will discuss the various causes of osteonecrosis of the knee with a special emphasis on spontaneous osteonecrosis and its role in the pathogenesis of OA of the knee in the elderly population.

Classification

Osteonecrosis of the knee may be classified as primary (idiopathic) or secondary, Table 1.[1 4 7 11 17]

Etiology and Pathogenesis

Vascular pathology is thought to play the major role in the development of secondary osteonecrosis of the knee.[7 11] The knee joint is particularly susceptible to ischemic insult because the subchondral bone of the femoral and tibial condyles is supplied by nutrient arteries with limited collateral circulation.[9 11 17] When the circulation in the terminal capillary of bed of the condyles is compromised, local anoxia and osteocytic death result. It is theorized that there is inadequate repair of this microdamage by osteoblasts and osteoclasts.[11] Further ischemia and more extensive necrosis can then lead to trabecular thinning, microfractures, and eventually, segmental subchondral bony collapse.[11]

Localized trauma, in the form of fractures, dislocations or epiphyseal separations in children, can interrupt the blood supply to the knee.[7 9 11 17]

It has been proposed by some investigators that excess systemic glucocorticoids (e.g. immuno-suppressive therapy in kidney transplant recipients) may lead to the development of a fatty liver which can shed fat emboli.[17] The fat emboli could lodge in the subchondral capillaries and other vessels and thereby decrease the blood flow to large portions of the femoral and tibial condyles.[7 11] This mechanism has also been suggested as the cause of osteonecrosis secondary to alcoholism, Gaucher's disease, and hyperuricemia.[7 11 17] In addition, excess glucocorticoids produce osteoporosis which predisposes the subchondral bone to traumatic injury.[7 10] Intra-articular injections of steroids have never been shown to cause osteonecrosis.[7]

The collagen-vascular diseases can

Table 1: Classification of Osteonecrosis of the Knee

Primary: Osteochondritis Dissecans - Juvenile
Spontaneous - Elderly

Secondary: Trauma.
Excess Glucocorticoids.
Steroid Therapy.
Cushing's Syndrome.
Collagen - Vascular Disease.
S.L.E.
Rheumatoid Arthritis.
Dysbarism (Decompression Sickness)
Hemoglobinopathies (S-S, S-C, etc.)
Metabolic Disorders.
Hyperlipidemia.
Gaucher's Disease.
Hyperuricemia.
Alcoholism.

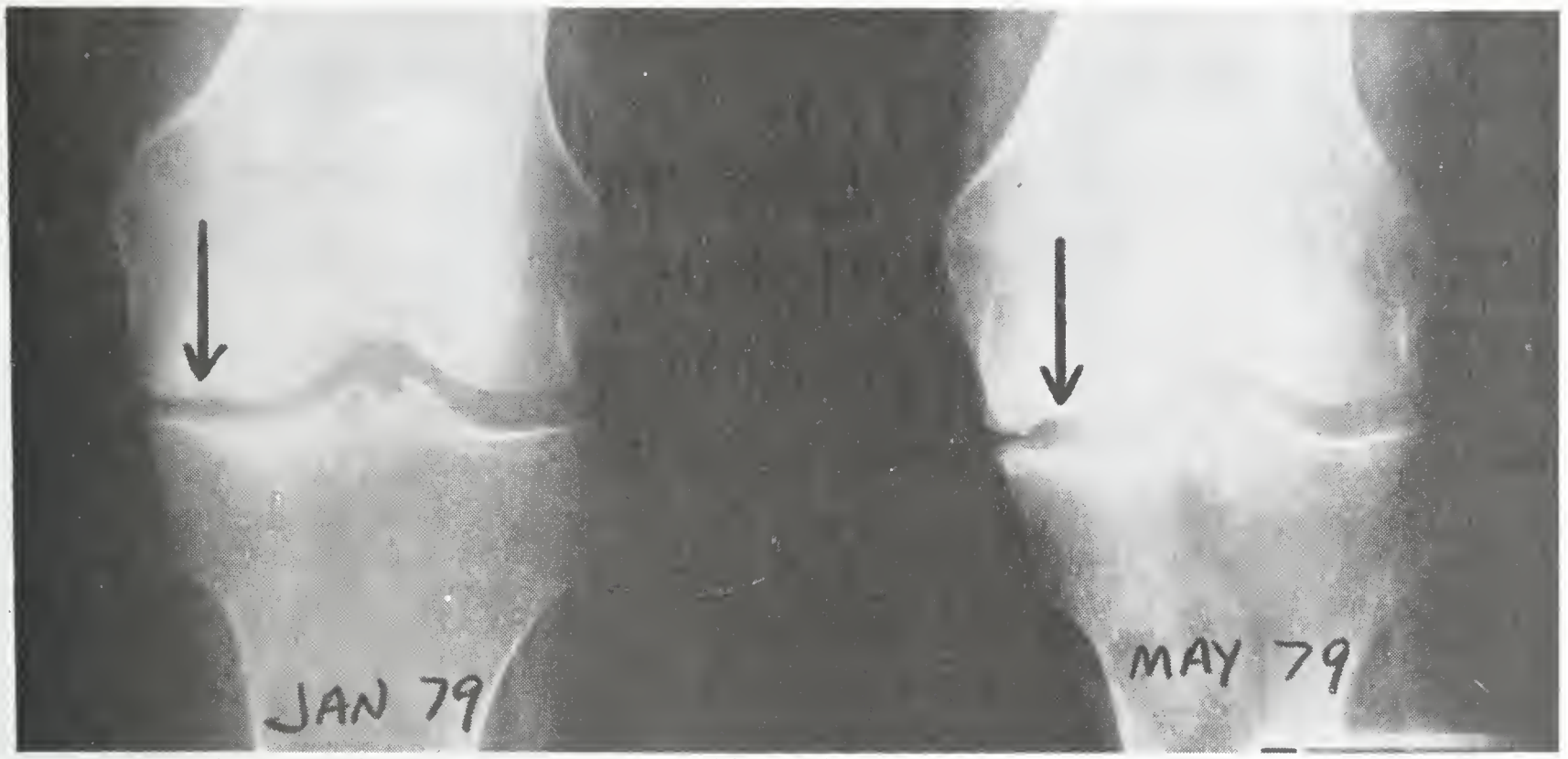

Figure 1: Serial X-rays of S.O.N.K. in a 75 year old female show in January '79 (left) flattening of the medial femoral condyle (arrow) with a crack in the articular cortex and minimal OA. In May '79 (right), there is a concave bone defect with a small subchondral lucency, sclerotic halo, and moderate OA. See the bone scan of this patient in Fig.4.

interfere with the blood supply of the knee due to vasculitis or as a consequence of the systemic steroids used in therapy.[7]

Dysbarism (decompression sickness) can occur in people who are exposed to sudden drops in atmospheric pressure (e.g. divers, compressed-air (tunnel) workers, and aviators.[7 11 17] The rapid decompression causes nitrogen bubbles to be released from solution in the blood.[11 17] These bubbles can embolize to the terminal vessels causing platelet aggregation, cellular clumping, lipid release, ischemia and bone cell death.[7 11 17]

In sickle-cell anemia or sickle-cell trait, deoxygenation of hemoglobin S causes the red blood cells to assume a rigid, elongated crescent-shape, and there is a marked increase in blood viscosity.[10 11] The above factors may then obstruct the flow in the small intraosseous vessels, leading to osteonecrosis.[11 17]

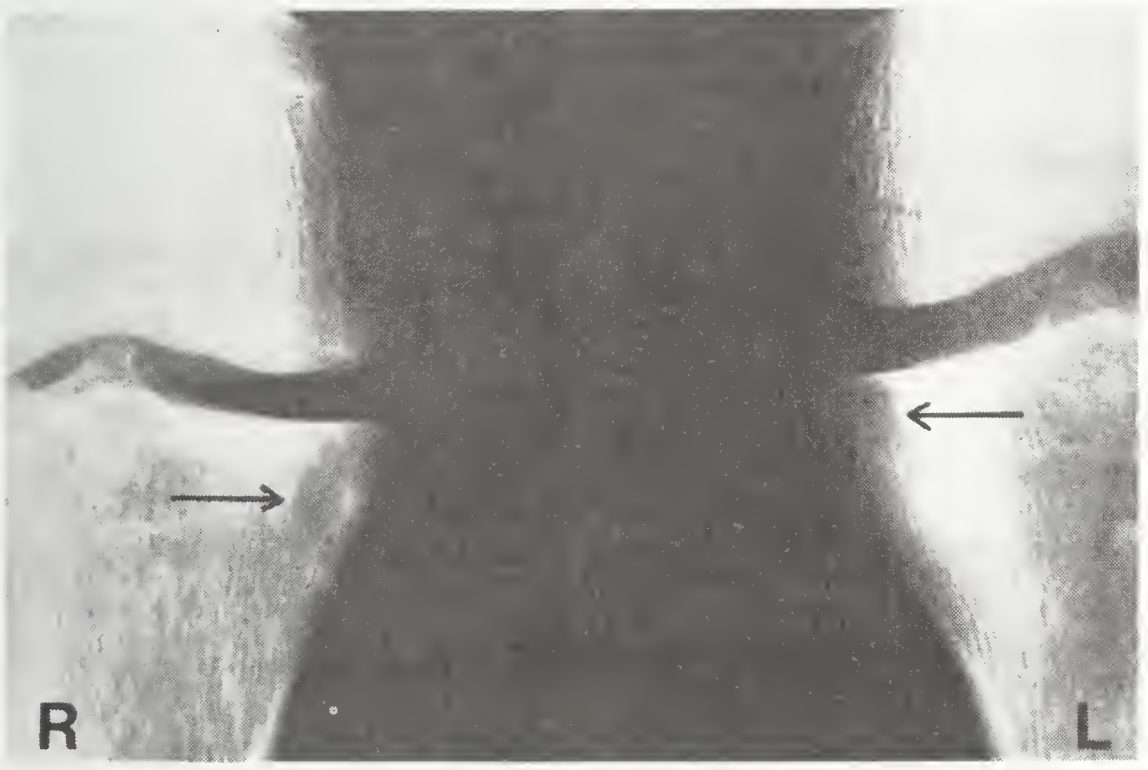

Figure 2: X-ray of S.O.N.K. in a 60 year old male shows bilateral subchondral cystic luencies in the medial tibial plateaus (arrows) with surrounding sclerosis and minimal OA. See the bone scan of this patient in Figure 5.

Hyperlipidemia accelerates the development of generalized atherosclerosis,[10] and thus predisposes the subchondral bone to ischemic damage via thrombosis or plaque emboli.

Although no clear etiologic factors have been implicated in the pathogenesis of primary osteonecrosis (i.e., osteonecrosis dissecans and spontaneous osteonecrosis), a number of theories have been proposed.

Osteochondritis dissecans, which tends to occur in adolescents and young adults, involves the subchondral bone on the lateral aspect of the medial femoral condyle.[1 2 18] End-artery thrombosis, trauma, and a congenital predisposition have all been suggested as possible etiologies.[1] The necrotic segment of bone often breaks off to form a loose body within the knee joint.[1]

Spontaneous osteonecrosis of the knee (S.O.N.K) tends to occur in patients over the age of 60, and involves the weight-bearing portion of the medial femoral condyle[2 18] (Fig. 1), or the most medial edge of the medial tibial plateau[12] (Fig. 2). These patients have no evidence of any of the conditions associated with secondary osteonecrosis. It has been proposed that age-related osteoporosis, generalized atherosclerosis, and medial shifts in

Figure 3: X-ray of severe OA and varus deformity in a 74 year old female who had presented 8 years earlier with minimal OA and S.O.N.K. in the medial femoral and tibial condyles. Note the concave bone defect in the medial femoral condyle (arrow).

weight-bearing in the knee predispose these individuals to microstress fractures of the trabeculae in the medial femoral or tibial condyles.[12 16] The microtrauma could then lead to osteonecrosis by disrupting the circulation in the local arterioles. Excessive bone resorption and propagation of the microfractures through the necrotic subchondral bone might complicate the healing process.[7] Collapse of the articular plate and the development or progression of OA are often the end result[3] (Fig. 3). However, in contrast to osteochondritis dissecans, loose bodies are rarely formed in S.O.N.K.[2 18] As well, the segment of the medial femoral condyle affected by osteochondritis dissecans is lateral to the area involved in S.O.N.K.[2 18]

Spontaneous Osteonecrosis Study

Materials and Methods

Sixty-five patients (77 knees) with S.O.N.K. were diagnosed at the Mount Sinai Hospital between the years 1968-1980.[13] These patients were assessed clinically, radiologically, and by radionuclide bone scan. Tissue was available for histological examination in six cases. Based on the medical history and complete blood work, none of these patients had any evidence of the conditions commonly associated with secondary osteonecrosis.

Forty-seven patients were females and eighteen were males. The average age for females at the time of onset was 70.3 years (range 50-86), and for males, 63.1 years (range 43-81). The fact that females outnumbered males by greater than 2.5:1, which agrees with other series,[18] might be due to two factors - senile osteoporosis, and the fact that more females are alive after age 60 as a result of longer life expectancies.[5] The right knee was affected 38 times, and the left knee, 39. The medial femoral condyle was involved in 59 knees, including 5 patients bilaterally. The lateral femoral condyle was affected in 1 patient (1 knee). The medial tibial plateau was involved in 21 knees, including 6 patients bilaterally. Two patients had S.O.N.K. in both the medial femoral and tibial condyles of the same knee whereas 3 other patients had contralateral involvement.

The patients were followed from 4 to 144 months (mean 34). Two died, one due to breast cancer, and the other from a CVA. The extent of osteoarthritis in the knee was graded radiologicaly as follows:[15]

None - No visible changes.
Minimal - Spurring of tibial spine, some flattening of the femoral condyles, minimal narrowing of the joint, and small marginal osteophytes.
Moderate - Appreciable narrowing of the joint space, subchondral sclerosis, and larger osteophytes.
Severe - Obliteration of the joint space with deformity, or even destruction of the articular surface with subluxation.

Clinical Presentation

The dominant symptom was severe pain, usually well-localized to the medial side of the knee. it appeared suddenly in 59 of 77 knees, and gradually in 18 of 77. Most of these patients were retired and did not participate in vigorous physical activity. The pain was aggravated by weight-bearing and was often present at rest. At the onset, when the pain was severe, the patient was quite disabled with regard to daily activities, and usually required a cane and moderate analgesics.

Physical examination revealed an effusion in 69 of 77 knees, and virtually all the knees were tender over the medial compartment. About one-half of the patients were obese. At the time of the first visit, a mild varus (bow-legged) deformity was noted in 24 knees and at follow-up visits, an additional 10 knees had developed a varus alignment. Flexion, although painful, was not significantly decreased at the onset. However, the range of motion decreased slightly in some patients at later visits due to the development of OA. Most of the patients had stable knees at the onset, but medial collateral instability eventually appeared in 15 knees due to significant narrowing of the medial compartment joint space.

Synovial fluid was obtained from 17 knees and was found to be clear with a normal cell count and no crystals.

Radiological Findings

The first x-ray changes of S.O.N.K. in our series could be identified one month after the onset in six patients, and after twelve months or more in the rest. However, in nine cases, radiological changes of osteonecrosis never developed in spite of the fact that they had a classical clinical presentation and a positive bone scan. The finding of normal x-rays and positive scans for S.O.N.K. has been reported in other series as well.[14 18]

The x-ray changes in spontaneous osteonecrosis of the medial femoral condyle were well-documented by Ahlback *et al.*[2] Identical changes may occur in S.O.N.K. involving the medial tibial plateau.[12] The first visible change is a flattening or slight depression of the weight-bearing surface of the medial femoral condyle (Fig. 1) or the most medial edge of the medial tibial plateau. Later, a linear or cyst-like subcondral lucency develops, which is believed

Figure 4: Bone scan of S.O.N.K. in the patient in Figure 1, done in Feb. 1979, shows increased uptake in the medial femoral condyle of the left knee. The right knee is normal.

Figure 5: Bone scan of S.O.N.K. in the patient in Figure 2, shows increased uptake in the subchondral bone of the medial tibial plateau in both knees.

to be due to microfractures through the necrotic bone,[7] and there is a reactive sclerotic halo (Fig. 2) The bony articular plate that covers the translucent area, may fragment or sink into the lucency, forming a concave bone defect. (Fig. 1) Rarely, the articular plate can break off to form a loose body. Loose bodies appeared in 3 of our cases but locking, as a result of this fragment, only occurred in one patient. The subcondral lucency may fill in, as occurred in one of our cases, but once a concave bone defect develops, there is permanent articular deformity.

The later development or progression of medial compartment osteoarthritis is common[2 4 18], and tends to be accelerated in patients with a larger necrotic lesion.[18] However, in patients that only have spontaneous osteonecrosis of the medial tibial plateau, there does not appear to be any acceleration in the development or progression of OA.[12] It should be noted that S.O.N.K. may develop in perfectly normal knees. In our series, 38 knees were normal at the onset, 26 had mild OA, 7 moderate, and 6 severe. Follow-up x-rays showed that 28 knees deteriorated significantly in terms of OA (Fig. 3), including 16 knees that had been previously normal. The presence of varus deformity and/or chondrocalcinosis tended to be associated with a more rapid deterioration. In fact, severe OA developed in 4 of 7 patients with chondrocalcinosis.

Scan Pattern

Radionuclide bone scans using either ^{99}m Technetium-labelled polyphosphate, or, after 1977, ^{99}m Technetium-labelled methylene diphosphate were done in 43 of our patients. Both anterior and medial views of each knee were taken with the gamma camera. In all these cases, the bone scan was positive immediately after the onset (Fig. 4), often months before any x-ray changes of S.O.N.K. appeared. In fact, as already stated, the scan was positive in 9 knees which never developed radiological evidence of osteonecrosis. As well, 2 of our patients had positive scans in the opposite asymptomatic knee, 18 months before any symptoms appeared, Therefore, the radionuclide bone scan is the most definitive procedure for diagnosing S.O.N.K.[4 8 18]

In the acute phase of the lesion, the bone scan shows increased uptake in the medial femoral condyle (Fig. 4) and/or medial tibial plateau (Fig. 5) This pattern persisted for months to years in many patients, but in one quarter of the cases, the uptake significantly decreased to a normal or an OA pattern[8] within one year.

It should be noted that stress fractures, which usually occur in the tibial condyles in younger and more athletic individuals,[6] also produce a similar increased uptake on the bone scan. However, the area involved in stress fractures[19] is usually much larger than that seen in S.O.N.K. (Figs. 5,6) Therefore, microstress fractures through the medial femoral or tibial condyles might be responsible for the localized subchondral uptake seen in spontaneous osteonecrosis.

Pathology

Tissue was obtained from six patients, and the histologic features were those of osteonecrosis[2 3 16 17] There were fragments of necrotic cancellous bone with empty osteocyte lacunae and apposed to it was viable new lamellar bone. Cartilaginous fracture callus and fibrovascular connective tissue in the bone marrow were also seen.

Treatment

At the onset, all the patients could not bear weight without experiencing severe pain, and they were helped by using a cane or crutches. Jones has suggested that decreased weight-bearing and avoidance of other mechanical stresses to the knee may prevent articular collapse and the progression of OA in some cases.[11] Analgesics and intra-articular injections of steroids were given to many patients for symptomatic relief but these did not appear to influence the course of the disease. Static exercises helped to prevent muscular atrophy, while motion increased the pain. In most patients, the acute symptoms settled in less than a year. Although one-third of the cases went on to develop significant osteoarthritis and continued to experience pain, it was much milder than the pain at the onset of S.O.N.K.

Surgical procedures were required in nine patients. Surgery is indicated when the symptoms persist due to marked collapse of the articular plate and/or progressive medial compartment OA leading to varus deformity and instability[18] The operative procedures consisted of 3

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Figure 6: Bone scan of right tibial stress fracture in a 31 year old male jogger shows increased uptake in the entire proximal tibia with the greatest uptake below the tuberosity.

high tibial osteotomies to shift the weight bearing to the lateral compartment, 1 curettage and bone grafting, and 5 condylar allografts.

Discussion

Spontaneous osteonecrosis must be considered in the differential diagnosis of the painful knee in the elderly.[2 4 14 18] Stress fractures meniscal tears, and osteoarthritis are the other important components of the differential diagnosis but the history, course, and bone scan can distinguish S.O.N.K. from these conditions.

The development or progression of OA of the knee occurred in one-third of our patients with S.O.N.K., and this correlated well with the series of Rozing *et al.*[18] Knees particularly at risk were those with a larger osteonecrotic lesion, previous varus alignment, and chondrocalcinosis. Patients that had S.O.N.K. involving only the medial tibial plateau appeared to have the best prognosis.

The relationship of spontaneous osteonecrosis to the pathogenesis of OA in the elderly knee must be examined more closely. Osteoarthritis of the knee, like S.O.N.K., most commonly involves the medial compartment.[10] Idiopathic OA, which usually begins after the fifth or sixth decade of life, is thought to have a more gradual onset and a more prolonged course[2 4] than S.O.N.K., which also tends to occur after ago 60. However, symptoms developed gradually in 18 knees with spontaneous osteonecrosis in our series, and 28 knees deteriorated significantly over several years. The radiological criteria for early OA include some flattening of the femoral condyle and associated sclerosis, which are also both x-ray changes seen in S.O.N.K. The proposed etiology for idiopathic OA is fatigue microfractures of the subchondral bone due to continued wear-and-tear on the joints, leading to increased forces on the articular cartilage and degererative changes.[10] Microstress fractures, as stated earlier, have also been suggested as the initiating event in spontaneous osteonecrosis. Therefore, there is a great deal of overlap between these two conditions. In fact, S.O.N.K. and OA may be on a pathological continuum with spontaneous osteonecrosis being one of the initial lesions in the development of osteoarthritis in the elderly knee.

Since X-ray changes of S.O.N.K. may take many months to appear, the diagnosis will often be missed unless a bone scan of both knees is done at the time of the initial visit. In fact, the opposite asymptomatic knee may be scan-positive for 18 months or more before symptoms ever develop, as was the case in 2 of our patients. Later, radiologic changes of S.O.N.K. may be obscured by the progression to moderate or severe OA, and the condition could be diagnosed as simply osteoarthritis. We believe that if elderly patients, with a history of medial compartment knee pain, were scanned as a matter of routine, the diagnosis of S.O.N.K. would be made more frequently, and treatment could be instituted earlier.

Conclusion

Spontaneous osteonecrosis of the knee was diagnosed in 65 patients with involvement of the femoral condyle in 60 knees, and the tibial plateau in 21. The average age of the patients was 68.3 years and the majority were females. Severe medial knee pain, aggravated by weight-bearing, was the dominant symptom. Radionuclide bone scan was the most definite diagnostic tool. Serial x-ray studies over several months to years were necessary to pick up any radiological changes of S.O.N.K. One-third of the knees developed significant osteoarthritis. We have suggested that S.O.N.K may be one of the initiating lesions in the pathogenesis of idiopathic OA. Therefore, painful knees in the elderly should be routinely scanned in order to diagnose and treat spontaneous osteonecrosis early, before it leads to irreversible joint deterioration. □

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Infant Formula And The Boycott of Nestlé's Products

The international boycott of Nestle's products is entering its fourth year with no sign of resolution. The goal of the boycott is to force Nestle to end its aggressive promotion of infant formula in Latin America, Africa and Asia. (Nestle is the largest marketer of formula in the Third World, with an annual sales volume of $200 to $250 million.) Organized in Canada by the Infant Formula Action Coalition (INFACT), the boycott has been endorsed by a broad spectrum of organizations, including the Canadian Council of Churches, the Association of Allied Health Professionals (Ontario), and OXFAM Canada.

It is estimated that six million babies in Third World countries are being fed infant formula. Critics of Nestle claim that these babies are at higher risk for infection and malnutrition than breast-fed babies. Formula confers no immune protection, and poverty, lack of sanitary conditions, and lack of a clean water supply, result in the preparation of dilute, contaminated formula. As U.S. Senator Edward Kennedy asked in 1978, "Can a product which requires clean water, good sanitation, adequate family income, and literate parents to follow printed instructions be properly and safely used in areas where the water is contaminated, sewage runs in the streets, poverty is severe, and illiteracy is high?"

Studies quoted by INFACT provide striking support for the claim that bottle-feeding represents a significant health hazard. For example, a study of Canadian Indians found that "Fully bottle-fed infants were hospitalized with infectious diseases 10 times more often, and spent 10 times more days in hospital during the first year of life than fully breast-fed infants...The protective effect, which lasted even after breast-feeding was discontinued, was independent of family size, overcrowding in the home, family income and education of the parents." (Ellestad-Sayed, J., *et al.*, *CMAJ* 120: 295-298, 1979). An investigation in Indonesia found that, in a sample of mothers using formulas, "One-third were less than 50% of proper strength...3/4 of the samples had bacterial densities in excess of 10,000 per ml...improper preparation of milk feeds leading to gross bacterial contamination and incorrect formula strength occurs in a substantial proportion of cases using bottle feeds..." (Surjono, D., *et al.*, forthcoming, *Journal of Tropical Pediatrics*).

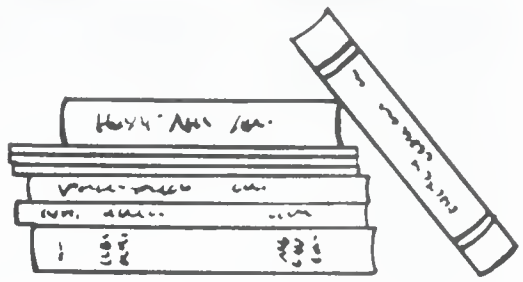
Nestle presently promotes infant formula in three ways. Blue-uniformed "medical representatives" speak to mothers directly, thus creating an impression of medical sanction for the use of infant formula. TV, radio and billboard advertisements show plump, smiling babies receiving formula. Supplies and free samples are distributed to medical facilities; the rationale behind this is explained in a document published by the United Church of Canada: "Free samples are provided to mothers in the hospital, and studies have shown that a mother is likely to continue to use a product that she believes carries a medical endorsement because of the environment in which she receives it...Hospitals and clinics in many developing countries are often poorly-equipped. Physicians may feel it justified to give away free samples of infant formula in exchange for a company's gift of medical stocks or a new nursery." ("Infant Formula Controversy", The United Church of Canada, winter 1979).

These promotional practices continue despite pressure from numerous groups, including the World Health Organization, which in 1979 recommended that all such practices be stopped. The International Baby Food Action Network (IBFAN) documented 202 violations of the WHO recommendations by Nestle and 19 other companies in 33 countries in just four months (January to April 1980).

Nestle's products include Taster's Choice, Encore, Quik, Montclair Mineral Water, Cherry Hill cheese, Beech-Nut Baby Foods, and Libby's. For more information on the boycott, contact INFACT, 85 St. Clair Ave. E., Toronto, 967-9195. □

Meldon Kahan 8T2

Book Review



Is Medicine Unfair To Women?

Connie Hsia 8T2

The Hidden Malpractice

How American Medicine Mistreats Women

By Gena Corea
(Jove/HBJ Books, $1.95, approx. 300pp.)

The highly revealing title of this book makes one immediately wonder whether one is dealing with yet another headline-grabber, the latest member on the merry wagon of physician-clobbers, or a genuine analysis of the state of modern medicine. The author, a former nurse's aide-turned-journalist, sets out to expose the crimes contrived by the medical profession (here synonymous with male dominance) in the U.S. against the feminine sex. Ms. Corea's deliberate cultivation of the shock value of the subject matter is evident right from the start. Throughout the book, she bombards our senses with outrageous statements, quotations, and examples of barbarous practices, allegedly reserved only for the female patients. However, it is a well-researched book, and many of her statements should provoke introspection among medical practitioners. The many anecdotes contained in the book will also make good reading for those interested in the history of medicine.

The major portion of the book deals with the male physician-female patient relationship. Here Ms. Corea's appetitie for the sensational is unsatiable. We are told, among other atrocities, of clitoridectomy and ovariotomies performed for such indications as " 'indigestion, insomnia, fissure of rectum, pain in the back or side, sterility, an inability to look one straight in the face, painful urination, melancholy, headache, a desire to run away from home or to become a nurse, heart palpitation, anemia, swollen joints, failing eyesight, dry skin and clammy skin.' " If a woman dislikes housekeeping and prefers a job as a telephone repairperson, Ms. Corea claims, then all her aches and pains shall be attributed to her "failure to accept the female role". She accuses physicians of punishing women who have contracted VD, by failing "to pass out VD handbooks to their patients, along with their pamphlets on the dangers of socialized medicine", and by failing to develop a gonorrhea vaccine for women. "Could it be," she asks, "that men do not view gonorrhea as a serious health problem because they are not as seriously affected by it as women are?"

Ms. Corea goes on to tell us that early attempts to introduce contraceptive methods were stalled by physicians who feared that contraception would reduce the number of their patients and leave them with nothing to do. But physicians would have no qualms about sterilizing the poor, the mentally retarded, or women belonging to ethnic minorities. Medicine, she charges, is practicing eugenics, i.e. the improvement of a race by selective breeding.

The "massive Pill experiment" is another subject under attack by the author. Most women know next to nothing about the complications of the Pill, she claims, thanks to their doctors who are almost as ignorant, and who are contented to let themselves be educated by the pharmaceutical industry. Facts about the Pill have been deliberately kept from women, so they will not reject oral contraception and thus threaten population control. Doctors, these modern-day eugenists, "would sacrifice the individual for a broader social goal".

Other accusations abound: doctors who sell sterilization as a package deal with abortion; doctors who perform a tubal ligation when C-section and then list it as an appendectomy; doctors who give postmenopausal women ungodly amounts of estrogen, and care not if they all get uterine cancer. Doctors who would prescribe the "morning-after" pill even though the dosage of DES is 55,000 times the amount the FDA tried to ban in cattle feed. On and on, the author tackles each aspect of modern medicine. Frequently citing individual cases, she then generalizes by saying, "this often happens" or "I've been told that many times". This pattern of

over-generalization considerably weakens the impact of her argument. As the reader's head spins with bewilderment, she ends the book by calling on women to organize themselves, to understand their own physiology, and to be more assertive where their rights are concerned.

Many of her arguments warrant closer attention. For example, she points out that in the field of contraception, there is a great deal of reluctance to develop a contraceptive pill for men; many researchers have stated that it is too dangerous to meddle with the male hormone balance. However, when it comes to manipulating the female hormones, such meddling does not seem to worry most researchers unduly. Particularly penetating is her analysis of the harmful effects of modern obstetrical practices. Many procedures, including needless cesarian sections, elective induction of labor, forceps extractions, and the undesirable lithotomy position, are performed more for the physician's convenience than the patient's comfort or interest. The author also advocates the wide acceptance of midwives in hospitals which, she claims, makes economical (midwives charge one tenth to one fifth the doctor's fee) as well as social sense to the majority of patients who have perfectly normal pregnancies and deliveries.

On the other hand, one must question Ms. Corea's biased presentation of her material. To read the book, one would be led to believe that no male physician could possibly truly care for the well-being of his female patients. By presuming that every action taken by the physician is determined by ulterior motives, and that sexual discrimination underlies all of women's sufferings, the author has cast both physician and patient into her own set of sterotypes. Modern medicine deserves a more balanced evaluation than that acknowledged by Ms. Corea. The prevailing negativism expressed in the book will certainly damage the physician's credibility, and further erode the doctor-patient relationship. Physicians are not to be trusted; they do not have your best interests in mind. This is the sour taste left by the book. Even female physicians, according to Ms. Corea, after being molded by their education and the desire to be accepted by their male colleagues, have adopted the values of the medical caste to become "honorary males", and cannot be depended upon to defend female patients against harmful practices. She then goes on to say, at the end of the book, that "it may not be enough to simply increase the number of female gynaecologists because the few men remaining in the field will rise to the top and control everything." Her solution? Male medical students should be banned from obstetrics and gynaecology. Coming from someone who seems determined to combat any form of sexual discrimination, this statement is more than ironic. It certainly does nothing to advance the feminist cause the author so heartily embraces. □

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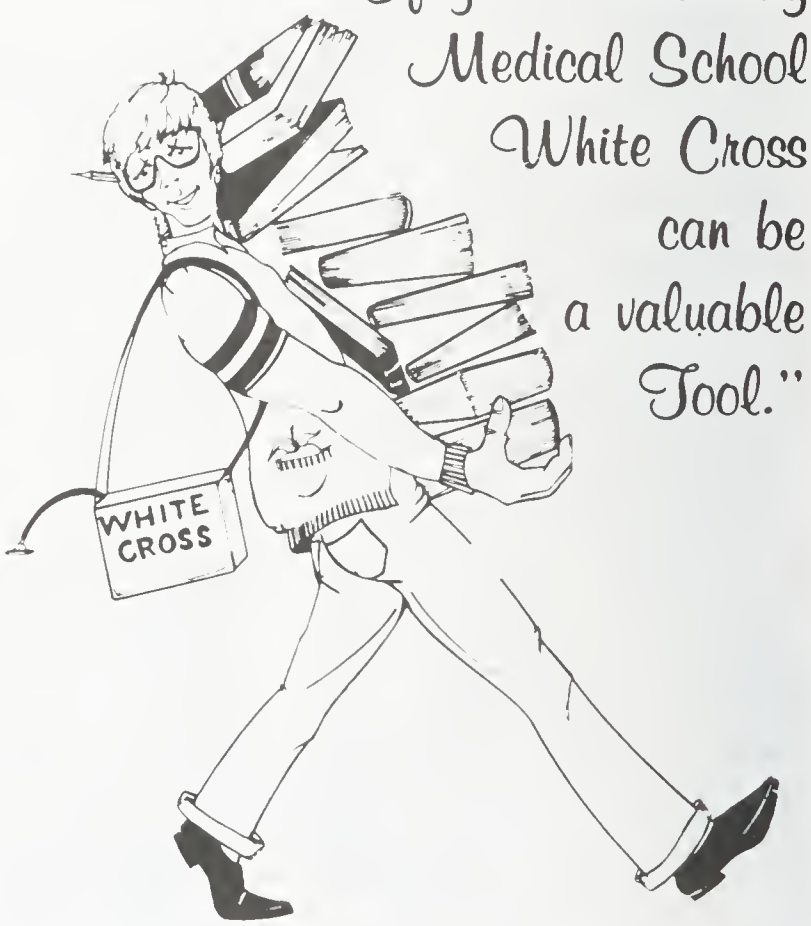

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together. As a piano needs a bench, so too medical expertise requires support personnel, supplies, and a place to work. The crucial aspect to this marketplace is that as well as being a supplier, the physician is also the demander. The nature of the doctor-patient relationship is such that the patient effectively gives over management of the illness to his agent, the physician.

The physician can perfectly match the demand and supply of his own service since he has control over both. This is a very real phenomenon. An overworked doctor can order a regimen which requires less of his own time (for instance by using nurses to administer drugs), and thus reduce "demand" by his patients to equal "supply" of his available time. Similarly, by urging elective surgery, he can increase the demand for his time if he is not as busy as he would like to be.

Whether or not physicians actually do this, the important implication is for the administrator, he cannot influence the demand for his own resources. That is, no matter what style or colour of piano the physician decides to order (and immediately deliver), the administrator must always have in stock a perfectly matching bench. In the hospital this means drugs, heart monitors, nurses, beds, supplies, special foods. electricity, paper, and so on. There is a very high price to pay when a patient deteriorates or even dies because some critical resource is unavailable due to poor administrative planning. Thus, administrators have a strong incentive to pour money into resources in order to ensure that space, support staff and supplies are available whenever a sick patient arrives in this marketplace and a physician begins to demand hospital resources to suit himself.

Two qualifying points need to be made here. First, the above discussion focuses only on one of many kinds of interactions between the two hierarchies. Second, the discussion ignores the very real effort made by administrators to exert moral suasion on the physicians to engender cost-consciousness in the latter, and the physicians' generally favourable response. The discussion does, however, point out a basic schism in the efficient management of an Ontario hospital, which is perpetuated by the high differential expertise of the two hierarchies, as well as their different relationships to forces outside the hospital.

Where Will They Go?

As hospital costs soar, there is greater pressure by society to improve the efficiency of these institutions. To the extent that the dual hierarchy is a useful model, then one of two courses must be chosen to lessen the gap in knowledge and decision-making between the two groups. Either administrators will begin to practise medicine in order to decrease ambiguity in resource-planning (an unlikely event), or physicians will become more directly involved in resource-planning.

A concept randomly selected from the health planning literature is something called cost-effectiveness analysis (CEA), a tool which is being rapidly adopted at all levels of decision-making. The objective of CEA is to structure and analyze information in a manner which will inform, and thereby assist, in decision-making. Rather than focusing on financial parameters such as internal rate of return, net present value, and other techniques quite foreign to the physician, CEA measure the outcomes of resource allocation in non-monetary units, such as "years of life saved" or "days of morbidity avoided".

Space constraints preclude elaboration of the approach, but it is one of the changes paving the way for the physician of the future to be more sensitive to the organization around him or her, and to take a more active role in running the doctor's hospital. □

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Baldness With Dignity

Robert Hegele 8T1

The prospect of going bald is a thought which probably crosses the mind of every healthy androgen-producing individual at some time in his life. There are some definite advantages to having a head which resembles a large cue-ball. For example, you have less hair to comb. The disadvantage of course is that you have more face to wash. Many people say baldness is a sign of evolutionary precocity; they believe bald people represent a higher form of life. However, the people who say this are usually bald. While the thought of one's parietal recession ending up in the occipital region may not be frightening to some, I am facing the inevitability of my own forehead spreading towards the nape of my neck with some concern. Luckily for people like me there is Dr. Elisabeth Rubler-Koss (with a hyphen) of Redneck State University in Illinois. Dr. Rubler-Koss (with a hyphen)—or Liz, as she is known to her friends and clients—has never personally experienced baldness, but her observations of 1043 males living through the psychological trauma of achieving skinhead-dom has enabled her to speak as an authority on the field (and off the field).

In her classic treatise *On Baldness and Balding*, Dr. Rubler-Koss successfully relates "what the balding have to teach doctors, nurses, the clergy and their own families". The American Journal of Testosterone-Related Changes (AJTRC) says of this revolutionary book: "...for those who take seriously the message to heal the sick and bury the bald, this book is a must...". Incidentally, Dr. Rubler-Koss (with a hyphen) has recently lost some measure of credibility after joining a bizarre Mexican cult which worships burritos and distributes literature on Montezuma's revenge on street corners in Acapulco. What follows is a summary of Ms. Rubler-Koss's now classic 5-stage model of the psychological changes associated with balding.

Stage I: Denial and Isolation

Among 1043 interviewed patients, most reacted to the awareness of terminal baldness, at first, with the statement: "No, not me. Those must be someone else's hairs in the sink!" They are convinced that the combs have been mixed up. Denial functions as a healthy way of dealing with the unfortunate and painful situation, but is temporary and is soon replaced by the second stage.

Stage II: Anger

When denial cannot be maintained, rage, anger and resentment set in. The patient asks: "Why me? I've always washed my hair every day. Why couldn't it have been Maurice? I mean, he has no morals. He kicks his dog and I've seen him take two newspapers out of the paperbox after paying for only one. And he is of no earthly value, as far as we mere mortals can tell. His job involves tightening the rubber bands on 29-cent plywood airplanes. He moonlights as a pin-setter at the Long Ball Bowling Alley, although he occasionally works the snack-bar." During this stage, the physician should be very diplomatic. One doctor recommended to an angry patient that he could take a job as an understudy to one of the Three Stooges. This unfortunate physician's face is now part of the Emergency Room wall at Toronto General. Anger is soon followed by the next stage.

Stage III: Bargaining

If the balding patient has been unable to accept the sad facts he may buffer his internal stress by entering into a magical "agreement" with some higher omnipotent force (e.g., God, or perhaps even a hospital administrator). He imagines that he may be rewarded for good behaviour. For example, Mr. G.L. donated all his worldly belongings, which included a broken soda glass and a set of green patio lamps, to the Church of Ecumenical Breadpins (the "Holy Rollers"), with the agreement that his baldness be delayed until after the completion of his upcoming marriage and honeymoon. Unfortunately, the church was taken to court when the founder (the Rev. Ken Baker) was discovered by police to be in a compromising position with a large sack of Robin Hood flour. As for Mr. G.L., his baldness became malignant rapidly, so that he was both alopecic and divorced by the end of his honeymoon.

Stage IV: Depression

As the terminally bald patient can no longer deny, or psychologically defend against his condition in other ways, a sense of great loss ensues. He realizes the huge waste of money and time his combs, shampoo and trips to the barber shop really were. He makes plans for the distribution of his personal haircare belongings, especially his Sunbeam blowdrier. Some become psychotically depressed. A.J. of Baltimore, Alberta, reports having had a recurring dream in which his head is discovered in an egg carton by Vidal

Sassoon. Mr. M.A.K. from Umbilicus, Wyoming, dreamed that his head was used in the construction of the Houston Astrodome. Once he imagined that his head was the model igloo in a new Eskimo subdivision. Mr. R.P. of Hubert, Ontario actually became so deranged that he shaved his wife's and all his children's heads. In most cases depression leads to the final stage.

Stage V: Acceptance

If a patient has had enough time (i.e. not a sudden, unexpected baldness) he will reach a stage during which he is neither depressed nor angry about his fate. He accepts the inevitable in several ways. For example, he can passively allow events to proceed, and bald naturally. Some choose to pursue a more active course, which may involve making appointments with Masterline or The Hair Barn. Some may seek medical help through hair transplantation. Most men learn to live with their baldness.

To conclude this review we present a partial transcript of an interview which Liz had with a patient who realized that he was terminally bald:

E.R-K: So, when did you first realize you were going bald?
Mr. H.: Get lost, lady.
E.R-K.: Uh huh. And how did this make you feel?
Mr. H.: Look, I told you. I don't want to talk about this.
E.R.-K.: That's interesting. Tell me, have you ever heard voices?
Mr. H.: I don't think you heard me lady. Bug off.
E.R.-K.: I see. Have you ever felt that people on television are talking directly to you?
Mr. H.: Is this being taped?
E.R.-K.: Have you ever thought of harming yourself?
Mr. H.: This is being taped, isn't it?
E.R.-K.: I understand. Did you have a happy childhood?
Mr. H.: Oh (expletive deleted) it's being taped. I see the microphone stuffed up your left nostril.
E.R.-K.: Okay. Would you say your parents were authoritarian and distant?
Mr. H.: I'm leaving...(muffled sounds)...misleading (expletive deleted)...(expletive deleted)...
E.R.-K.: I see. This is something you don't like to talk about is it, Mr. H.?

(continued from page 87)

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